American Heart Journal

An international publication for the study of the circulation

GEORGE E. BURCH, M.D.
Editor

HARRY L. COLCOLOUGH, M.D.
NICHOLAS P. DePASQUALE, M.D.
JOHN H. PHILLIPS, M.D.
Assistant editors

1430 Tulane Avenue, New Orleans, La. 70112
The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103

VOLUME 75

JANUARY-JUNE, 1968

VOLUME 75

Printed in the United States of America

American Heart Journal

JANUARY 1968

Contents

continued on page 3

left-sided heart failure: initial symptoms ...but no obvious signs

Diamox®

Acetazolamide

Tablets 250 mg

In the early milder forms of decompensation DIAMOX provides the moderate diuretic action needed Fluid loss is maintained at a gentle pace that eases patients back into balance with little change in normal electrolytes. A single morning dose achieves peak effects during the day allows uninterrupted nighttime rest.

Contraindications—Situations in which sodium and/or potassium serum levels are depressed, kidney and liver diseases or dysfunction, suprarenal gland failure and hyperchloremic acidosis Long-term administration is contraindicated in chronic noncongestive angle closure glaucoma.

Warning—Although teratogenic and embryocidal effects demonstrated in mice at more than ten times the equivalent therapeutic doses have not been evidenced in humans, DIAMOX Acetazolamide should not be used in pregnancy especially during the first trimester unless the expected benefits outweigh these potential adverse effects.

Precautions—Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Reactions common to sulfonamides may occur: fever, rash, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis. If such occur discontinue drug and institute appropriate therapy.

Side Effects—During short term therapy: paresthesias, loss of appetite, polyuria, drowsiness, confusion. [illegible] long-term therapy an acidotic state may supervene. Transient myopia has been reported. Other occasional reactions: urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, convulsions.

LEDERLE LABORATORIES A Division of AMERICAN CYANAMID COMPANY Pearl River N.Y. Lederle

Contents *continued*

Experimental and laboratory reports

Case reports

Review

continued on page 5

MEDTRONIC Uses X-Ray "Before and After" for Quality Assurance

The use of X-ray in the Medtronic implantable device manufacturing sequence is basic in the company's quality control program. First of all electronic components and batteries are X-rayed as they are received to verify absence of electrical deterioration and manufacturing defects. Then after each Medtronic device is completed, aged and packaged, the entire shipping carton is X-rayed again to check battery quality and integrity of the package. This X ray is kept for record.

X ray therefore, is an important before and after tool in Medtronic's quality control program. X ray is so important that Medtronic uses custom equipment and procedures for handling everything from transistors to complete shipping cartons.

Quality assurance is a vital function at Medtronic so vital that entire departments are devoted to maintaining quality control and reliability assurance at every step in implantable device manufacture. An important adjunct to the use of X ray is the technique of random selection and destruction of one percent of each shipment of batteries and other electronic components to verify their certification to Medtronic standards. One percent of finished products also is held and placed into simulated body fluid baths for life testing.

X-ray and other quality control techniques are only a few of the steps in reaching Medtronic's goal of supplying implantable devices of the highest possible standards. Medtronic, for example puts serial numbers on pulse generators and electrodes and records lot serial numbers of each shipment of components and batteries. Standardization also is achieved by documenting on the implantable device package the date of final inspection and testing, date of sterilization, temperature limits and, on pacemakers, their rate at body temperature.



Medtronic, Inc

[illegible] HIGHWAY EIGHT MINNEAPOLIS, MINNESOTA [illegible]

AREA 612/[illegible]

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

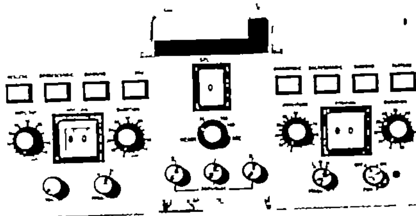
Annotations

Vol. 75, No. 1, January, 1968. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. *Annual subscription rates*—United States and its possessions: institutional (multiple-reader) subscriptions, $21.00*; personal (regular) subscriptions,† $16.00; student, intern, and resident physician subscriptions,† $9.60. Canada and Mexico: institutional (multiple-reader) subscriptions, $21.50; personal (regular) subscriptions, $16.50; student, intern, and resident physician subscriptions, $12.50. Other countries: institutional (multiple-reader) subscriptions, $24.50; personal (regular) subscriptions, $19.50; student, intern, and resident physician subscriptions, $13.10. Single copies, $2.50 postpaid.

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics; city, county, state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals. Second class postage paid at St. Louis, Mo.

A New Approach to Aid in Teaching Auscultation



PhonoCardioSimulator HEART SOUND TRAINING AID

SIZE 11½ X 5¼ X 17" WEIGHT 25 POUNDS

The PhonoCardioSimulator provides the medical instructor with complete flexibility in the production of sounds and murmurs. All normal and abnormal heart sound patterns along with an ECG signal are automatically generated electronically and can be presented to an unlimited audience via stethophones, oscilloscopes or oscillographs.



Please send PhonoCardioSimulator information to

NAME

ADDRESS

CITY STATE ZIP

American Heart Journal

FEBRUARY 1968

Contents

Editorial

Clinical communications

continued on page 3

Contents continued

continued on page 3

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews

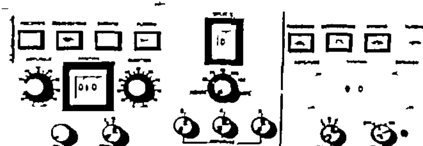
Vol. 7[illegible], No. 2, February, 1968. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. *Annual subscription rates*—United States and its possessions: institutional (multiple-reader) subscriptions,* $21.00; personal (regular) subscriptions,† $14.00; student, intern, and resident physician subscriptions,† $9.00. Canada and Mexico: institutional (multiple-reader) subscriptions, $22.50; personal (regular) subscriptions, $15.50; student, intern, and resident physician subscriptions, $11.50. Other countries: institutional (multiple-reader) subscriptions, $24.00; personal (regular) subscriptions, $19.50; student, intern, and resident physician subscriptions, $12.50. Single copies, $2.50 postpaid.

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics; city, county, state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

A New Approach to Aid in Teaching Auscultation



PhonoCardioSimulator HEART SOUND TRAINING AID

Pat. Pend.

SIZE 11½ X 5¼ X 17" WEIGHT 25 POUNDS

The PhonoCardioSimulator provides the medical instructor with complete flexibility in the production of sounds and murmurs. All normal and abnormal heart sound patterns along with an ECG signal are automatically generated electronically and can be presented to an unlimited audience via stethophones, oscilloscopes or oscillographs.



UMETRICS

TELEPHONE [illegible]

[illegible] AVENUE LOS ANGELES, CALIFORNIA [illegible]

Please send PhonoCardioSimulator information to

NAME

ADDRESS

CITY STATE ZIP

American Heart Journal

MARCH 1968

Contents

continued on page 3

When his decompensation is moderate, shouldn't his diuretic be, too?

Frequently, the answer is "yes"

For continuing therapy DIAMOX provides the moderate diuretic action needed in the early milder forms of congestive heart failure. Fluid loss is maintained without flood-tide diuresis, but rather with gentle action. A single morning dose provides peak action in the daytime hours, allows an uninterrupted night's sleep. Significant alteration of electrolyte balance is rare and can usually be controlled by adjusting dosage.

DIAMOX®
(Acetazolamide)


LEDERLE LABORATORIES
A Division of American Cyanamid Company
Pearl River, New York

Contraindications: [illegible]

Warnings: [illegible] DIAMOX Acetazolamide [illegible] effects.

Precautions: [illegible]

Side Effects: [illegible]

Contents continued

continued on page 5

Contents *continued*

Annotations

Book reviews

Announcement

Vol. 75, No. 3, March, 1968. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions, institutional (multiple-reader) subscriptions,* $[illegible].00; personal (regular) subscriptions,† $16.00; student, intern, and resident physician subscriptions,† $9.00. Canada and Mexico: institutional (multiple-reader) subscriptions, $21.50; personal (regular) subscriptions, $18.50; student, intern, and resident physician subscriptions, $11.10. Other countries: institutional (multiple-reader) subscriptions, $24.50; personal (regular) subscriptions, $19.50; student, intern, and resident physician subscriptions, $13.50. Single copies, $1.50 postpaid.

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics, city, county, state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions and all student rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

A NEW approach for the timing of heart sounds!



Right: The PCT is used in conjunction with the stethoscope and thus provides a visual signal which precisely places the stethoscopic sounds in the cardiac cycle

Below: The PCT requires a three-electrode connection to the patient.





For exact correlation of a stethoscopic sound with its associated light, one can cover any light or combination of lights with the fingertips.



The PCT obtains the required operating power from its detachable, rechargeable plug in battery unit.

PhonoCardioTimer Pat. Pend. HEART SOUND TIMING AID

The PhonoCardioTimer (PCT) is an electronic unit which indicates with display lights the time location of the first sound (S_1) second sound (S_2) systole and diastole as they occur regardless of heart rate



UMETRICS — Thiokol CHEMICAL CORPORATION

TELEPHONE (213) 477-4567
2212 BARRY AVENUE LOS ANGELES CALIFORNIA 90064

Humetrics Division,
Thiokol Chemical Corporation
2212 BARRY AVENUE / LOS ANGELES, CALIFORNIA 90064

Send information to:

NAME

ADDRESS

CITY STATE ZIP

American Heart Journal

APRIL 1968

Contents

continued on page 3

Contents *continued*

Experimental and laboratory reports

Case reports

Clinical pathologic conference

Fundamentals of clinical cardiology

continued on page 8



MEDTRONIC Uses X-Ray "Before and After" for Quality Assurance

The use of X-ray in the Medtronic implantable device manufacturing sequence is basic to the company's quality control program. First of all, electronic components and batteries are X rayed as they are received to verify absence of electrical deterioration and manufacturing defects. Then after each Medtronic device is completed, aged and packaged, the entire shipping carton is X rayed again to check battery quality and integrity of the package. This X-ray is kept for record.

X-ray therefore is an important "before and after" tool in Medtronic's quality control program. X-ray is so important that Medtronic uses custom equipment and procedures for handling everything from transistors to complete shipping cartons.

Quality assurance is a vital function at Medtronic — so vital that entire departments are devoted to maintaining quality control and reliability assurance at every step in implantable device manufacture. An important adjunct to the use of X ray is the technique of random selection and dissection of one percent of each shipment of batteries and other electronic components to verify their certification to Medtronic standards. One percent of finished products also is held and placed into simulated body fluid baths for life testing.

X-ray and other quality control techniques are only a few of the steps in reaching Medtronic's goal of supplying implantable devices of the highest possible standards. Medtronic, for example, puts serial numbers on pulse generators and electrodes and records lot serial numbers of each shipment of components and batteries. Standardization also is achieved by documenting on the implantable device package the date of final inspection and testing, date of sterilization, temperature limits and, on pacemakers, their rate at body temperature.



Medtronic, Inc

3055 HIGHWAY EIGHT MINNEAPOLIS, MINNESOTA 55418

AREA 612/781-6855

Contents continued

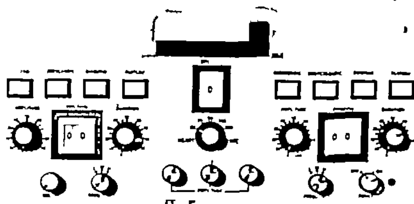
Vol. 75, No. 4, April, 1968. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions: institutional (multiple-reader) subscriptions, $21.00; personal (regular) subscriptions,† $16.00; student, intern, and resident physician subscriptions,† $9.00. Canada and Mexico: institutional (multiple-reader) subscriptions, $22.50; personal (regular) subscriptions, $16.50; student, intern, and resident physician subscriptions, $11.10. Other countries: institutional (multiple-reader) subscriptions, $24.50; personal (regular) subscriptions, $19.50; student, intern, and resident physician subscriptions, $13.10. Single copies, $2.50 postpaid.

Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals and clinics, city, county, state, province, and national government bureaus and departments and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

A New Approach to Aid in Teaching Auscultation



PhonoCardioSimulator HEART SOUND TRAINING AID
Pat. Pend.

SIZE 11½ X 5½ X 17" WEIGHT 25 POUNDS

The PhonoCardioSimulator provides the medical instructor with complete flexibility in the production of sounds and murmurs. All normal and abnormal heart sound patterns along with an ECG signal are automatically generated electronically and can be presented to an unlimited audience via stethophones oscilloscopes or oscillographs

UMETRICS Thiokol Chemical Corporation

TELEPHONE (213) 477-4987
LOS ANGELES, CALIFORNIA

Please send PhonoCardioSimulator Information to

NAME

ADDRESS

STATE ZIP

American Heart Journal

MAY 1968

Contents

continued on page 3



Frequently, the answer is "yes"

For continuing therapy DIAMOX provides the moderate diuretic action needed in the early milder forms of congestive heart failure. Fluid loss is maintained without flood-tide diuresis, but rather with gentle action. A single morning dose provides peak action in the daytime hours, allows an uninterrupted night's sleep. Significant alteration of electrolyte balance is rare and can usually be controlled by adjusting dosage.

DIAMOX®
(Acetazolamide)

LEDERLE LABORATORIES
A Division of American Cyanamid Company
Pearl River, New York

[illegible]

[illegible]

[illegible]

[illegible]

Contents *continued*

continued on page 5

Contents *continued*

Annotations

Letters to the Editor

Book reviews

Announcements

Vol 75, No [illegible] May 1968. American Heart Journal is published monthly by The C V Mosby Company 3207 Washington Blvd St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions: Institutional (multiple-reader) subscriptions, $21.00 personal (regular) subscriptions† $16.00 student, intern, and resident physician subscriptions† $9.00. Canada and Mexico: Institutional (multiple-reader) subscriptions, $21.50 personal (regular) subscriptions, [illegible] student, intern, and resident physician subscriptions, $12.10 Other countries: Institutional (multiple-reader) subscriptions, $24.50 personal (regular) subscriptions $19.50 student, intern, and resident physician subscriptions, $13.50. Single copies, $2.50 postpaid

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics, city, county, state, province, and national government bureaus and departments, and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the name of, and billed to, individuals.

Second class postage paid at St. Louis, Mo

Printed in the U. S. A.

Cont

Editorial

Clinical communications

Experimental and laboratory reports

con inued on r

Contents *continued*

continued on page 5

Contents

Vol. 75, No. 6, June, 1968. American Heart Journal is published monthly by The C. V. Mosby Company 3207 Washington Blvd St Louis, Mo 63103. Annual subscription rates—United States and its possessions: institutional (multiple-reader) subscriptions $21.00 personal (regular) subscriptions† $ 4.00; student, intern, and resident physician subscriptions† $9.00. Canada and Mexico: institutional (multiple-reader) subscriptions, $21.80 personal (regular) subscriptions $18.80, student, intern, and resident physician subscriptions, $12.10. Other countries: institutional (multiple-reader) subscriptions, $24.00 personal (regular) subscriptions, $19.80; student, intern, and resident physician subscriptions, $13.10. Single copies, $3.50 postpaid.

*Institutional (multiple reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics, city county state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

Printed in the U S A Copyright © 1968 by The C. V Mosby Company

A
NEW approach
for the timing
of heart
sounds!

Right: The PCT is used in conjunction with the stethoscope and thus provides a visual signal which precisely places stethoscopic sounds in the cardiac cycle

Below: The PCT requires a three electrode connection to the patient.



For exact correlation of a stethoscopic sound with its associated light, one can cover any light or combination of lights with the fingertips.



The PCT obtains the required operating power from its detachable rechargeable plug in battery unit.

PhonoCardioTimer — HEART SOUND TIMING AID

The PhonoCardioTimer (PCT) is an electronic unit which indicates with display lights the time location of the first sound (S_1) second sound (S_2) systole and diastole as they occur regardless of heart rate

HUMETRICS / Thiokol CHEMICAL CORPORATION

TELEPHONE (213) 47 567
2212 BARRY AVENUE / LOS ANGELES, CALIFORNIA 90064

Humetrics Division,
Thiokol Chemical Corporation
2212 BARRY AVENUE / LOS ANGELES, CALIFORNIA 90064

Send information to:

NAME

ADDRESS

CITY

STATE

ZIP

American Heart Journal

January 1968 Volume 75 Number 1

Editorial

Viral nephritis

G. E. Burch, M.D.
S. C. Sun, M.D.
New Orleans, La.

The high incidence of chronic nephritis in patients without an antecedent history of acute nephritis or of a streptococcal infection with an apparent associated renal disease has long been recognized. In fact the natural history of glomerulonephritis is becoming increasingly complex and little understood. This is due in large part to the fact that most adults with chronic nephritis present no history of acute and previous renal diseases from which to date the onset of their renal diseases. Furthermore, the relationship between poststreptococcal acute nephritis in children and chronic nephritis remains unknown. It is generally assumed that chronic renal disease begins with an unrecognized attack of acute nephritis during childhood precipitated by a streptococcal infection. This assumption, though common, is poorly supported by data. Furthermore, although the incidence of severe streptococcal infections of the nasopharyngeal region is declining, the incidence of chronic renal disease remains high.

The frequent occurrence of viral infections during childhood and throughout life and our recent observations of clinically occult Coxsackie B viral myocarditis and valvulitis in infants and children at routine autopsies[2-4] introduce a strong possibility that inadequately defined or unrecognized viral infections of the kidney may be etiologically concerned with renal disease. Thus direct viral infection of the kidney may produce acute, subacute, or chronic renal disease. Furthermore, it is possible that viruses may remain lodged and dormant in the kidneys to be awakened by a traumatic experience, including a streptococcal tonsillitis, to produce acute, subacute, or chronic active nephritis.

There are very similar clinical features of chronic valvular disease in patients without a history of previous acute rheumatic fever. Our recent investigations by means of immunofluorescent techniques revealed antigen of Coxsackie B viruses in the myocardium and heart valves of both adult and young patients with no clinical evidence of a specific viral infection or unusual streptococcal infection.[4] It is rather interesting that both chronic nephritis and chronic valvulitis and myocarditis offer the same difficulties etiologically and both are related to streptococcal infections.

The immunofluorescent technique has

From the Department of Medicine of the Tulane University School of Medicine, New Orleans, La.
Supported by grants from the United States Public Health Service.
Received for publication Aug. 2, 1967.

been applied to studies of the nature of glomerular disease states. These studies were concerned with hypersensitivity mechanisms in which the demonstration of gamma globulin and a component of complement as possible factors in the pathogenesis of a variety of glomerular disease.[4] However there has been very little application of the immunofluorescent techniques to identify the primary etiologic agent responsible for diseased kidneys. Streptococcal substance presumably an antigen combined with antibody has been demonstrated within glomeruli in post streptococcal glomerulonephritis[7] whereas others[8] have been unable to identify streptococcal antigen in the diseased kidney of man studied by biopsy and immunofluorescent technique

From existing knowledge of renal physiology it is not surprising that with streptococcocemia the bacteria either free or bound with antibody would be trapped in the glomeruli and produce infection Under such circumstances one might expect focal nephritis rather than diffuse glomerulonephritis Moreover the renal lesion in the parasitic infection of malaria has recently been shown to be due to the fixation of an antigen-antibody complex in the glomeruli.[8,9] During a viremia trapping and fixing of the viral particles in the kidney would be expected Viruses that are highly nephrotropic could then produce serious damage to the kidneys. That this could occur is evident when it is realized that essentially 20 per cent of the cardiac output flows through the kidney and primate kidney cells are excellent tissue culture material for many viruses infectious to man

A report of autoimmune reaction and viruslike particles in germ free NZB mice by East and associates[1] suggests the possible role of viral infection in triggering autoimmune disease Renal lesions similar to chronic membranous glomerulonephritis or lupus nephritis have been reported frequently in these mice.[1] East and associates[10] suggested that the virus could act directly as an endogenous antigenic stimulus to abnormal immunologic activity or by acting directly modify either tissue antigen or lymphoid cell function and thereby evoke autoimmune reactions. Our observations of the kidneys of experimental mice infected with Coxsackie B_4 virus support such possibilities. With the use of hyperimmune rabbit antiserum

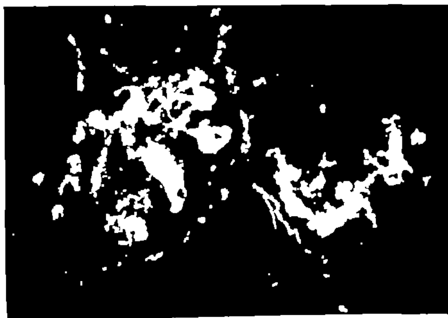


Fig. 1 Bright fluorescence the glomerular tuft of mouse experimentally infected with Coxsackie B virus 7 week previously Th section w treated with ti-mouse-globuli goat serum labelled with fluorescein. The fluorescent sites localize mouse globulin (X480).

against Coxsackie B virus and goat anti serum against mouse globulin both labelled with fluorescein the specific Coxsackie B viral antigen and globulin were demonstrated in the glomeruli of kidneys 6 to 8 weeks after infection with Coxsackie B virus (Figs. 1 and 2). The histologic examination of the kidneys revealed increased cellularity of the glomeruli and scattered focal areas of necrosis of renal tubules. Coxsackie B viral antigen was also identified in necrotic foci of the renal medulla.

Besides the probably complicated autoimmune phenomena during the viral infection which could result in renal damage it is also possible and even likely for the viruses themselves to damage the kidney tissue directly to produce the renal lesions. Benyesh Melnick and co-workers reported the recovery of latent viruses by cell cultures from kidney tissue in children. The kidneys could harbor latent viruses which might chronically irritate renal tissue or even be dominant and eventually become activated to cause overt renal disease in later life.

A survey of viral nephritis caused by Coxsackie B group and several selected types of ECHO viruses from routine autopsies by the immunofluorescent technique is underway. We have already found Coxsackie B viral antigen in the renal glomeruli and interstices of two (Figs. 3 and 4) patients studied at routine autopsy. One patient a 2-year-old Negro girl died of traumatic brain concussion and another a 48-year-old Caucasian woman had hypertension.

These data indicate that certain types of viruses may play an etiologic role in chronic glomerulonephritis. However the extent importance, and mechanism by which viruses can injure the kidneys need investigation. The concept is certainly worthy of study especially when it is realized that viral infections are so prevalent and the pathogenesis of nephritis and nephropathy are poorly understood and confused. Virologist, pathologist, and clinician have neglected considerations of nephrotropic viruses as possible important etiologic agents of renal disease in man.

That a viral infection can produce renal disease as one of its characteristic manifestations has been established for example Aleutian disease (AD) of mink and hemorrhagic fever. Proliferative changes in the stalk and mesangial portions of the



Fig. 2 Bright intracytoplasmic fluorescence in the cells of glomerular tuft of the same infected mouse as for Fig. 1 after treatment with anti-Coxsackie B virus rabbit serum labelled with fluorescein. The fluorescent sites localize Coxsackie B virus antigen. (×480.)



Fig. 3. Bright i tracytoplasmic fluorescence shown in the glomerula tuft of 2 year-old Negro girl who died of brain concussion t the Charity Hospital and was studied t routine topsy. The section was treated with anti Coxsackie B rabbit serum labelled with fluorescein. The fluorescent sites localize Coxsackie B iral tigen (×780.)



Fig. 4. Bright fluorescence hypercellula glomerulus of 48-y ar-old Caucasia woma with hypertension. The kidneys were collected t routine topsy t the Chair ty Hospital. The section was treated w th ti-Coxsackie B rabbit antiserum labelled w th fluorescein. The fluorescent sites localize Coxsackie B iral tigen (×780.)

glomeruli with thickening of the capillary basement membrane occurs with AD. Hyalin lesions in the glomeruli are constant findings. Accumulations of PAS-positive material as well as smooth, dense, nodular masses resembling lesions of the glomeruli in man are found in AD of mink. Gamma globulin also accumulates in the glomeruli. Capillary thrombosis in the glomeruli as well as tubular degenerative lesions likewise occur in AD. The histologic changes in AD of mink resemble very closely lesions commonly found in man with nephropathy (e.g., lupus erythematosus disseminatus, periarteritis nodosum) without clinically detectable etiology.

Thus, if renal disease can be produced in man by certain viruses, then viral nephropathies in general need careful and extensive investigation. Because of the favorable features of renal cells of primates as tissue culture material for viruses, the large volume of viremic blood that flows through the glomeruli during viral infections and the filtering function of the glomeruli would support the likelihood of viral infections of the kidneys of man.

REFERENCES

1. Barnett, H. L. Paediatric nephrology. Scientific study of kidneys and their disease in infants and children, Arch. Dis. Child. 41:229, 1967.
2. Burch, G. E., Sun, S. C., Colcolough, H. L., Sohal, R. S., and DePasquale, N. P. Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques, Am. Heart J. 74:13, 1967.
3. Burch, G. E., Sun, S. C., Chu, K. C., and Sohal, R. S. Interstitial myocarditis and Coxsackie B viral myocarditis in infants and children. A comparative histologic and immunofluorescent study of 50 autopsied hearts. To be published.
4. Burch, G. E., and DePasquale, N. P. Viral endocarditis, Am. Heart J. 67:721, 1964.
5. Freedman, P., and Markowitz, A. A. Gamma globulin and complement in diseased kidney, J. Clin. Invest. 41:328, 1962.
6. McCluskey, R. T., Vassalli, P., Gallo, G., and Baldwin, D. S. An immunofluorescent study of pathogenic mechanisms in glomerular disease, New England J. Med. 274:695, 1966.
7. Seegal, B. C., Andres, G. A., Hsu, K. C., and Zabriskie, J. B. Studies on pathogenesis of acute and progressive glomerulonephritis in man by immunofluorescein and immunoferritin techniques, Fed. Proc. 24:100, 1965.
8. Ward, P. A., and Conran, P. B. Immunopathologic studies of Simian malaria, Mil. Med. 131:1225 (Suppl.), 1966.
9. Dixon, F. J. Comments on immunopathology, Mil. Med. 131:1233 (Suppl.), 1966.
10. East, J., Prosser, P. R., Holborow, E. J., and Jaquet, H. Autoimmune reactions and virus-like particles in germ-free NZB mice, Lancet 1:755, 1967.
11. Helyer, B. J., and Howie, J. B. Spontaneous auto-immune disease in NZB/BL mice, Brit. J. Haemat. 9:119, 1963.
12. Hicks, J. D., and Burnet, F. M. Renal lesions in the autoimmune mouse strains NZB and F1 NZBxNZW, J. Path. & Bact. 91:467, 1966.
13. McGiven, A. R., and Hicks, J. D. The development of renal lesions in NZB/NZW mice: immunohistological studies, Brit. J. Exper. Path. 48:302, 1967.
14. Benyesh-Melnick, M., Rosenberg, H. S., and Watson, B. Viruses in cell cultures of kidneys of children and congenital heart malformations and other diseases, Proc. Soc. Exper. Biol. & Med. 117:452, 1964.
15. Karstad, Lars. Aleutian disease, a slowly progressive viral infection of mink, *in* Current topics in microbiology and immunology, New York, 1967, Springer-Verlag, Inc., vol. 40, pp. 9-21.
16. Smorodintsev, A. A., Kazbintsev, L. I., and Chudakov, V. G. Virus hemorrhagic fevers. Published for the National Library of Medicine, U. S. Public Health Service through the National Science Foundation, Washington, D. C.

Clinical communications

Pacemaker vectorcardiography

Agustin Castellanos, Jr., M.D.
Louis Lemberg, M.D.
Louis Sulkanick, M.D.
Ba[illegible] Berkovits, E.E.
Coral Gables, Fla.

Ventricular complexes induced by electric pacemakers differ from those produced by the normal supraventricular impulses which are conducted via usual A-V pathways. In 1930 Barker, McLeod, and Alexander showed that stimulation of one ventricle resulted in QRS complexes resembling those appearing after sectioning the opposite bundle branch. This, however, was considered an oversimplification. Recently Lister and associates recorded the morphology of the QRS complexes produced by stimulating different parts of both ventricles. They emphasized that each pacemaker site produces a distinctive pattern of ventricular activation. There are few reports dealing with the vectorcardiographic aspects of ectopic (natural or pacemaker) beats in the human heart. Analysis of loops obtained from patients with implantable (epicardial or transvenous) pacemakers was made in order to help establish the validity of the experimental assumptions. The importance of the vectorcardiogram in determining the location of the stimulating electrodes could also be assessed.

Material and methods

Twenty patients with implantable pacemakers were studied. Left ventricular epicardial units were used in 10. Seven of these were of the fixed rate type. The remaining 3 patients in this group had atrio-synchronized units.† Permanent transvenous implantation in the right ventricular apex was employed in 9 cases. One patient in this latter group had an epicardial right ventricular demand type pacemaker.‡

Complete electrocardiograms and vectorcardiograms (Frank system) were obtained in all patients. The recording apparatus consisted of a Sanborn Vector amplifier and Viso Scope, from which multiple pictures were obtained with a Polaroid Land Camera. The right sagittal plane was invariably used. All loops were photographed at X10, X5, and X2 amplifications (1 mv. equaled 1 inch at the X10 position). The following parameters were analyzed after projecting the frames on a large screen: spatial orientation, duration, and voltage of the maximal deflections of the stimulus artifacts, orientation of maxi

From the Section of [illegible] Department of Medicine, [illegible] of Miami School of Medicine, The Division of [illegible] Jackson Memorial Hospital, Miami, Fla., and the Department of Cardiology, Veterans Administration Hospital, Coral Gables, Fla.

Received for publication Feb. 21, 1967.

*Medtronic, Inc., Minneapolis, Minn.

†Cordis Corporation, Miami, Fla.

‡American Optical Company, Chelsea, Mass.

mal QRS and T vectors orientation of any initial mid, or terminal delay present in the spatial QRS loop. The values of these localized delays were considered abnormal if their duration exceeded 20 20 and 30 msec. respectively.[9,3] Vectorcardiograms were recorded 3 days to 6 months after implantation. There were 4 cases in which a fixed-rate pacemaker was coacting with the patient's own sinoatrial rhythm. This resulted in two basic types of loops, the morphology of which depended on whether the ventricles were depolarized completely by the artificial pacemaker or by the oncoming supraventricular impulses. Varying degrees of fusion beats were seen. These resulted from simultaneous, but unequal activation of the ventricles by both stimuli. The type of

Text continued on page 12

Table I. Data on patients with left ventricular pacemakers

Case N	Type	Stimulus artifact†	Initial delay	Horizontal (QRS loop)			Frontal (QRS loop)			Sagittal (QRS loop)		
				O	Ro	Delays	O	Ro	Delays	O	Ro	Delays
1	AS	L P I	R A S	RP	8	I (Pt T)	RS	8	I T	PS	8	I (Pt T)
2	FR	R P I	R P	RP	C-CW	I (Pt T)	RI	CW	I T	PI	CW	I (Pt T)
3	FR	R P I	R I	RP	8	IMT	ES	8	IMT	PS	8	IMT
4	FR	R A S	L A I	RA	CW	I T	RI	CW	I T	AI	8	I T
5	AS	R P I	L A S	RP	CW	I T	RI	8	I T	PI	CW	I T
6	FR	R P I	L A S	RP	8	I T	RI	8	I T	PI	8	I T
7	FR	R P I	A P I	RP	CW	I T	RI	8	I T	PI	8	I T
8	FR	R P I	L A S	RA	8	I T	RI	CW	I T	PI	8	I T
9	FR	R A S	R P I	RP	CW	I (Pt T)	RS	CW	I T	PS	CW	I (Pt T)
10	AS	R P I	R P S	RA	8	I (Pt T)	RI	CW	I (Pt T)	AI	CW	I (Pt T)

*FR = Fixed rate; AS = atriosynchronized; D = demand; L = left; R = right; A = anterior; P = posterior; I = inferior; S = superior; O = orientation of maximal QRS vector; Ro = rotation of QRS loop; I = initial; M = mid; Pt = preterminal; T = terminal; CW = clockwise; 8 = figure of eight; C-CW = counter-clockwise.
†Orientation of maximal deflection of spike.

Table II. Data on patients with right ventricular pacemakers

Case No.	Type	Stimulus artifact†	Initial delay	Horizontal (QRS loop)			Frontal (QRS loop)			Sagittal (QRS loop)		
				O	Ro	Delays	O	Ro	Delays	O	Ro	Delays
11	FR	R P I	I L A	LP	8	M T	LS	8	M T	PS	CW	M T
12	FR	R P S	I L P	LP	C-CW	I M	LS	C-CW	I M	PS	8	I M
13	FR	P S	I L P	LP	CW	I M T	LI	8	IMT	PI	C-CW	IMT
14	FR	R P S	I L A	LP	C-CW	IMT	LI	8	IMT	PI	8	IMT
15	FR	L A S	R P	LP	8	I T	LS	8	I M	PS	CW	I M
16	FR	R P S	I L	LP	8	IMT	LI	C-CW	IMT	PI	8	IMT
17	FR	R P S	I L A	RP	8	M T	RS	CW	M T	PS	CW	IMT
18	FR	R P S	I L A	LP	8	IMT	LS	8	IMT	PS	8	IMT
19	FR	L P S	I L P	LP	8	M T	LS	C-CW	M T	PS	CW	M T
20	D	R P I	I L P	LP	8	M T	LS	8	M T	PS	8	M T

*See footnote to Table I.

SA

SA

SA

HORIZONTAL FRONTAL SAGITTAL

I II III aVR aVL aVF

V1 V2 V3 V4 V5 V6

Fig. 1. Left ventricular (fixed rate) pacemaker. The vectorcardiogram shows CW rotation in the horizontal and frontal planes. There is a significant delay of all the efferent and of the terminal part of the afferent, loops. The T loop is opposed to the QRS loop. The small stimulus artifact (S A) points anteriorly, to the right and superiorly. The ST-T loop is rounded and shows partial (to plane) absence of the usual more rapid speed of inscription of its terminal portion. In the electrocardiogram there is right axis deviation associated with right bundle branch block pattern. There are ST-T wave changes suggestive of subendocardial ischemic injury and (or) digitalis effects. The areas of delay and slurring are best seen in the vectorcardiogram.



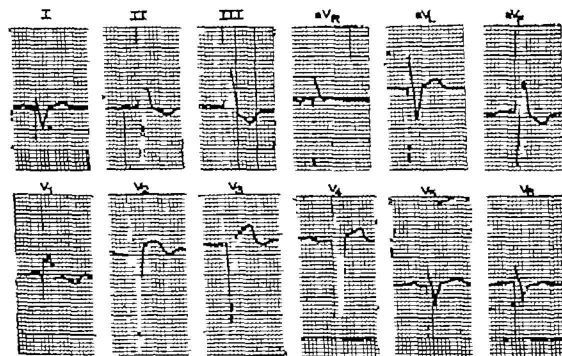
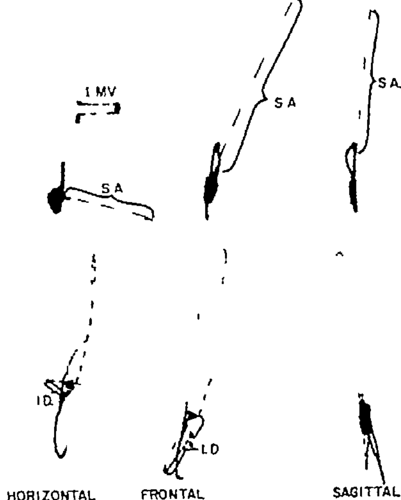


Fig. 2. Left ventricular (triosynchronized) pacemaker. In the vectorcardiogram there is CW rotation in the horizontal plane. The major part of the loop is located posteriorly, to the right, and inferiorly. The significant initial delay (*I.D.*) and terminal slurrings are clearly seen. The large stimulus artefact is oriented to the right, inferiorly and posteriorly. In the electrocardiograms the major abnormalities consist of right axis deviation and a right bundle branch block pattern in V. The atrio pacemaker conduction time measures 0.18 sec. The interval is much shorter in Lead V1, which was recorded during a period of pacemaker escape (from sinus control).



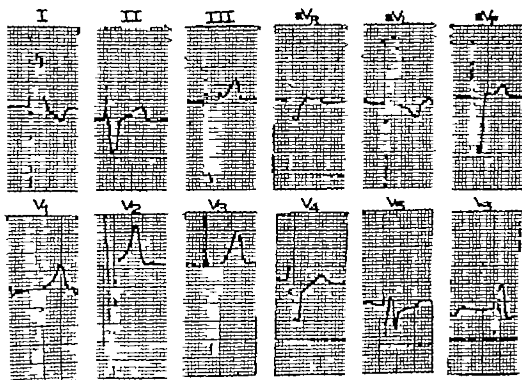
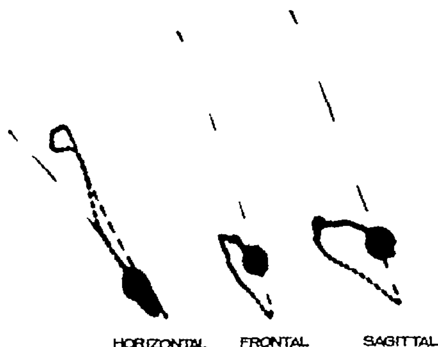


Fig. 3 Right ventricular endocardial pacemaker In the vectorcardiogram the stimulus artefact are oriented to the left superiorly and slightly anteriorly The QRS loop show an initial delay associated with a spatial (two plane) mid delay or plateau Similar types of loops have been described in patients with W P W coexisting with left bundle branch block.[14] There is left axis deviation in the electrocardiogram. Leads I aVL and V show a left bundle branch block morphology with a significant mid slurring



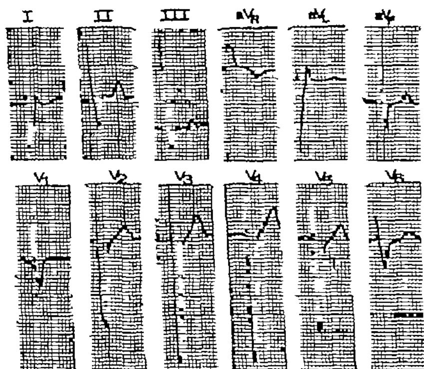


Fig. 4 Right ventricular stimulation producing a right axis deviation. In the vectorcardiogram the horizontal loop is located to the right and posteriorly. This type of orientation is usually seen in patients with left ventricular pacemakers. The electrocardiogram shows an S_1 S_2 and S_3 pattern. Both V_1 and V_6 show negative deflections, in keeping with the right posterior location of the QRS loop.

QRS complex obtained from the oscilloscope screen was also recorded and therefore identified in an electrocardiogram obtained at the same time Leads V_1 or V_{4R} were employed for this purpose

Results

Left ventricular pacemakers In patients the maximal spatial deflections of the stimulus artifact was located to the right, posteriorly and inferiorly (Table I) The corresponding voltages ranged between 0 2 and 12 mv The spikes usually consisted of a sharp deflection lasting from 10 to 20 msec A spatial (two plane) initial slurring greater than 20 msec was observed in all cases (Figs 1 and 2) This delay was *not uniform for 3 patients* showed varying degrees of slurrings throughout its extension There was no specific predilection for the spatial orientation of these delays. The major part of all QRS loops was oriented to the right of point E (Fig 1 and 2) They pointed posteriorly and inferiorly in 7 out of the 10 cases Clockwise or figure of 8 rotation was seen in the three planes. Counterclockwise rotation was seen once in the horizontal plane A spatial terminal delay greater than 30 msec was present in all cases This delay had preterminal accentuation (slurring in 4 patients The ST T loop was invariably opposed to the QRS loop

Right ventricular pacemakers The stimulus artifacts were oriented posteriorly and superiorly in 8 patients and located either to the right (in 1) or to the left (in 2) (Table II) In one case it pointed toward −90 degrees in the frontal plane. The corresponding voltages and duration ranged between 0.25 and 10 mv and between 15 and 20 msec. respectively A significant initial delay was seen in 8 cases. This delay was located inferiorly and to the left in all cases except one. Only one showed diffuse irregularities (slurring) throughout its extension. The QRS loops were oriented posteriorly and to the left nine times (Fig 3) In one case it was located in the right posterior quadrant (Figs. 4 and 5) The corresponding maximal vectors could point either superiorly or inferiorly Although the three basic types of rotation were seen in all planes, there was some predilection for figure of 8 rotation in the horizontal plane. A terminal delay oriented to the left was seen in 9 patients. It was associated with a mid plateau (or slurring) in 8 cases. A constant feature was spatial opposition between QRS and ST T loops. Cases 12, 13 14 and 16 showed an *independent sinus rhythm. In* 3 of them the vectorcardiograms of the natural beats were considered to be characteristic of right bundle branch block according to standard criteria.[11,12] One of these patients showed as an additional feature an inferoposterior wall myocardial infarction (Fig 6) Case 6 had complete left bundle branch block (Fig 7) Various degrees of fusion beats were seen in all instances of simultaneous independent *rhythms, including the case in which both* sinus and pacemaker beats displayed a left bundle branch block pattern (Figs. 5 and 7) These combination complexes depended on the amount of ventricular muscle activated by each pacemaker Stimuli falling in the absolute refractory period of sinoatrial beats were not followed by QRS complexes. In these cases it was usual for them to fall during the inscription of the QRS loop



Fig 5 Location of the endocardial catheter in the patient showed in Fig 4. The tip is believed to be placed in the right ventricular apex. Conventional x-rays and cinefluoroscopy were obtained a few minutes after the vectorcardiogram

Discussion

The spatial location of the maximal vector of the stimulus artifacts was of moderate diagnostic value. It is true that a right posterior and inferior orientation was seen in 70 per cent of the patients with left ventricular pacemakers. However, an identical type of orientation was present in 70 per cent of the spikes produced by right ventricular electrodes. Moreover, 50 per cent of the patients in the latter group also showed spikes pointing to the right although posteriorly and superiorly. The variations in stimulus artifact location were ascribed to the different sites of implantation and orientation within each ventricle. Another important factor was the variable location of the negative electrode in regards to the one with positive polarity. This relationship might be especially significant in cases in which unipolar rather than bipolar stimulation was used, since in these cases the vector of the spike might be different than when bipolar stimulation is performed with the same electrode and in the same ventricle. In favor of these assumptions is the change in orientation of the stimulus artifacts which can occur after wire breakage. This is seen if the distal end of the severed wire touches the body in a different site so that the flow of current from the negative to the positive terminal proceeds in a different direction than originally.

The initiation of the QRS loop frequently did not coincide with the point of origin of the stimulus artifacts (base line of the scalar electrocardiogram). This phenomenon, which has been ascribed to the diphasic characteristic of the spike, seemed to be more marked whenever uni-

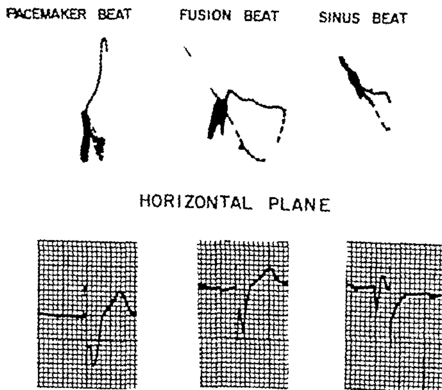


Fig. 6. Right ventricular pacemaker in a patient with sinus rhythm, right bundle branch block, and infero-posterior infarction. The vectorcardiogram at the left and its corresponding scalar recording (V_{OE}), show a left bundle branch block morphology. The natural beats, at the right, are compatible with the diagnosis of right bundle branch block and posterior wall infarction. The latter is suggested by the horizontal loop which has an abnormal anterior displacement associated with CW rotation. Combination complexes (middle row) are intermediate in contour between the pure natural and artificial complexes.

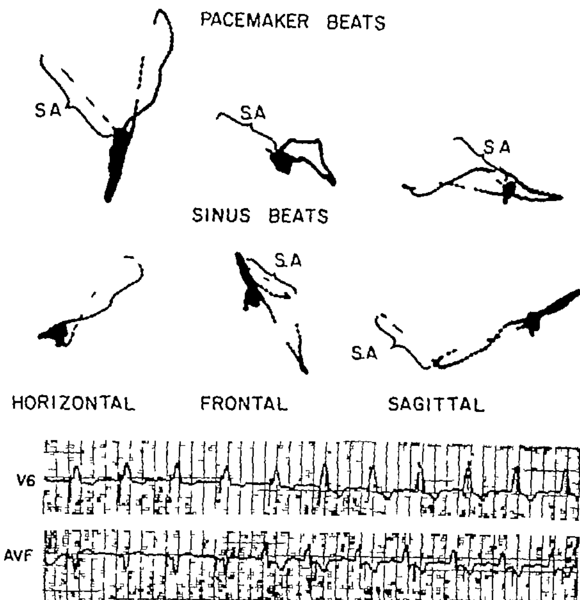


Fig 7 Right ventricular pacemaker in a patient with sinus rhythm and complete left bundle branch block The pure pacemaker beats (upper row) show spike oriented to the right superiorly and posteriorly Thus, not all stimulus artefacts produced by right ventricular pacemakers point toward the left, as shown in Fig 3. The loops are similar but not identical to those considered characteristic of organic left bundle branch block (lower row). The differences are more marked in the frontal nd sagittal planes. In addition the natural QRS loops in these planes are interrupted by the stimulus artifact which occurs t varying intervals after the onset of entricular depolarization The QRS complexes seen during the first half of the scalar recordings (Leads V nd \ F) are pure pacer beats. They are preceded by stimulus artifacts. The sinus beats (with LBBB) are seen toward the end of the tracings. The spikes are now falling within the QRS complexes. Note that the differences between natural nd artificial entricular complexes are more marked in a\ F than in \ Left xis deviation occurs only during artificial stimulation of the heart

polar stimulation has been employed It has been implied that it is sometimes difficult to determine the precise moment in which ventricular activation starts. In 90 per cent of the cases presented in this communication a short transition between the fast component of the stimulus artifact and the relative slow initial part of ventricular depolarization could be identified in the enlarged frames.

According to Buchner and associates[8] the accuracy of assessing the beginning of

depolarization by such a method has been confirmed by their phonocardiographic studies in patients with implanted pacemakers. These authors also considered that in certain occasions, especially when unipolar subpectoral pacemakers were used a capacitive artifact could arise triggered by a condensor like postdischarge of the muscular tissues between the stimulating and recording electrodes. In such cases it would be difficult to determine (electrically) the initiation of ventricular activity. There is evidence in favor of the intramyocardial versus the extramyocardial origin of the significant initial delay. Lister and associates[2] studied the sequence of electrical activation of the dog's ventricles from different sites. They found a more or less synchronous excitation of large areas of the epicardial surfaces. It was believed that a large mass of ventricular muscle was activated through the conducting system. By studying ingeniously constructed ventricular excitation maps they explained the differences required for ventricular depolarization on the basis of the amount of muscle mass activated by muscle conduction immediately after delivering the artificial impulse. The time required by the stimulating front to enter the major branches of the conducting system was a contributing factor. Impulses from several sites, even within one ventricle entered the contralateral ventricle through different routes.

The initial delay produced by pacemaker stimulus is similar to the one seen in patients with W P W syndrome. Both W P W complexes and pacemaker induced beats produce early vectorial changes generated when excitation starts ectopically in the ventricles at variable distance from the normal A V junction and peripheral Purkinje's fibers. It is interesting to note that whereas an initial delay was observed in all instances of epicardial electrodes, it was absent in 2 patients in whom endocardial catheters were used presumably because of an early activation of the conducting system which in the latter cases could be closer to the stimulating electrodes.

Simultaneous presence of initial and late delays in the vectorcardiograms can have other causes besides electrical stimulation of the myocardium. These double conduction disorders have been described in cases of W P W associated to bundle branch block, in intrainfarction block complicated by periinfarction block[13,14] and in simultaneous coexisting left ventricular focal and right bundle branch block. The association of W P W with peri-infarction block is theoretically possible since the former affects the initial vectors and the latter the terminal part of the loop. This combination has not been reported.

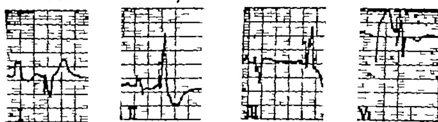
The gross morphology of the resultant QRS loops depended on the site of stimulation. The beats induced within the left ventricle were invariably oriented to the right. The anterior or posterior spread of activation was dependent on whether implantation was made in the postero-lateral or anterolateral aspects of the left ventricle. Similarly frontal plane orientation was dependent also on the inferior or superior attachments of the electrodes. In general the loops resembled those recorded from patients with sinus rhythm and complete right bundle branch block although in these cases the terminal delay is located usually anteriorly, rarely posteriorly. The latter orientation is more common when right bundle branch block coexists with right ventricular hypertrophy.

The morphology of beats triggered from the right ventricle were similar to those recorded in cases of complete left bundle branch block, although with some minor differences. In the patient with coexisting sinoatrial and implanted pacemakers who also had organic left bundle branch block the artificial and natural beats showed significant discrepancies (Fig. 6). The differences were not as marked in the leads recording the horizontal (X) axis of the dipole (Leads I and X). Both horizontal and frontal planes showed changes consistent with initial right-to-left spread of activation during both natural and artificial beats. It is interesting to note that the former were oriented inferiorly whereas the pacemaker loops were directed superiorly. This indicates that there is a specific type of septal depolarization in complete left bundle branch block which cannot be duplicated by stimulating at

random any area of the right septal surface. This case illustrates clearly that complete left bundle branch block by itself is an infrequent cause of abnormal left axis deviation.[1, 14] Stimulation of the right ventricular apex, on the other hand, can be included with other causes of abnormal left axis deviation. This anomalous orientation has been reported in the following conditions: (a) block of the superior division of the left branch, whether due to anterolateral infarction,[20] subendocardial fibrosis,[20-24] cardiomyopathies,[25] or congenital malformations;[26, 27] (b) inferior wall myocardial infarction;[1] (c) pulmonary emphysema;[1, 29] (d) hyperkalemia; the Wolff-Parkinson-White syndrome.[31, 34]

The presence of fusion beats in instances of double rhythms indicates that the ventricles are depolarized from two different pathways. Various combinations were seen whenever iatrogenic parasystoles fused with natural beats (Fig. 6) even in the patient with simultaneous organic and artificial left bundle branch block (Fig. 7).

In one case stimulation of the right ventricular apex yielded QRS complexes which resembled those originating in the anterior aspects of the left ventricle. At first it was considered that the catheter had perforated the interventricular septum and was lying inside the left ventricular cavity. Multiple x-ray studies, including cinefluoroscopy, showed that the tip of the distal electrode was impinged in the right ventricular apex (Fig. 5). These findings indicate that stimulation of the anterior portion of the heart, slightly to the right or to the left of the interventricular septum, can produce resultant forces which are



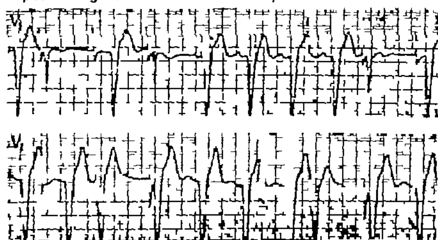


Fig. 8. False pattern of left ventricular stimulation by electrode located within the right ventricular cavity (records obtained during transient transvenous pacing). The upper strips were recorded at a time in which the x-rays had shown that the catheter was coiled inside the right ventricular cavity. There is competition between natural beats with left bundle branch block morphology and the iatrogenic complexes which, at this moment, display a right bundle branch block pattern. Repositioning of the catheter within the right ventricle yielded transition morphologies in the middle strip. Finally in the lower strip both sinoatrial and artificial QRS complexes show a left bundle branch block pattern.

oriented posteriorly and to the right. In our department we have observed another case in which transient bipolar stimulation inside the right ventricular cavity produced QRS complexes with a right bundle branch block morphology. This is shown at the top of Fig. 8 recorded at a time that the catheter was coiled inside the right ventricle. Careful repositioning of the catheter produced a progressive change from the unexpected right bundle branch block morphology to the expected left bundle branch block appearance. It seems that in rare cases the exact location of the tip of a transvenous electrode cannot be definitely ascertained by the morphology of the iatrogenic QRS complex. These discrepancies had been noted by several authors who studied the electrocardiographic morphology of artificial extrasystoles. Abramson and associates[11] found that in monkeys, stimulation of the high right ventricular conus could produce beats with a right bundle branch block appearance. In a detailed investigation of the electrocardiographic features of extrasystoles produced in various areas of the dog's ventricles, Nahum, Hoff, and Kaufman[20] postulated that right ventricular premature beats could occasionally fail to produce an upward deflection (complete left bundle branch block morphology) in Lead I. This was particularly liable to occur if the stimulated area was close to the septum and propagation took place in such a fashion that a major part of the left ventricle was activated at the same time as the right. According to Scherf and Schott,[21] the type of QRS complex after forced beats depends not only on the site of stimulation but to some extent on the direction of the electrical axis and in anatomic rotation of the heart as well.

Summary

The spatial vectorcardiograms of 20 patients with implanted pacemakers were studied. Ten had left ventricular and 10 right ventricular units. The orientation of the stimulus artifacts did not prove to be an important parameter in the distinction between each type of instrument. The spikes appeared as a sharp deflection which lasted more than the accepted value of 2.5 msec. Initial delays, attributed to conduction through ordinary cardiac muscle, was seen in all patients with left ventricular and in 8 of the patients with right ventricular pacemakers. The morphology of the loops elicited by left ventricular stimulation resembled vectorcardiograms considered diagnostic of right bundle branch block with or without right ventricular hypertrophy. Beats originating in the right ventricle yielded vectorcardiograms similar to those seen in cases of left bundle branch block. One patient had an independent sinus rhythm with left bundle branch block; both natural and artificial QRS loops were similar but not identical. This case showed that artificially induced apical beats, but not necessarily left bundle branch block, can display abnormal left axis deviation. One patient with an implanted right ventricular pacemaker showed an electrical axis oriented to the right. Since the same phenomenon was seen in another case during transient intracardiac pacing, it seems that stimulation of the anterior region of the heart either slightly to the left or to the right of the interventricular septum can yield QRS complexes oriented to the right and posteriorly. Hence the morphology of the QRS loop is not an infallible criterion for locating the position of the stimulating electrodes.

REFERENCES

1. Barker, P. S., McLeod, A. G., and Alexander, J.: The excitatory process observed in the exposed human heart. Am. Heart J. 5:720, 1930.
2. Lister, J. W., Klotz, D. H., Jomain, S. L., Stuckey, J. H., and Hoffman, B. F.: Effect of pacemaker site on cardiac output and ventricular activation in dogs with complete heart block, Am. J. Cardiol. 14:494, 1964.
3. Duchosal, P. W., and Sulzer, R.: La vectorcardiographie, Basel, 1949, S. Karger AG.
4. Donzelot, E., Milanovich, J. B., and Kaufman, H.: Etudes practiques de vectorgraphie, Paris, 1950, L'Expansion Scientifique Française.
5. Massie, E., and Walsh, T.: Clinical vectorcardiograph and electrocardiography, Chicago, 1960, Year Book Medical Publishers.
6. Buchner, CH., Bilger, R., Overbeck, W., Streicher, CH., and Reindell, H.: Das Elektrokardiogramm und Vecktorkardiogramm nach Implantation eines Elektrischen Schrittmachers, Ztschr. f. Kreislaufforsch. 54:861, 1965.
7. Lepeschkin, E., and Zao, A. Z.: Comparison between the anatomical orientation of stimulating electrodes and the spatial direction of electric potentials prod[illegible] them in pa[illegible]

tients with implanted pacemakers, presented at the Seventh I ter-American Congress of Cardiology, Montreal P Q Canada, June 14-19 1964

8. Frank, F An accur t linically practical system of spatial vectorcardiogr phy Circulation 13 737 1956
9. Mayer J W Castellanos, A Jr and Lemberg L The patml ector rdiogr m in peri-infarction block Am. J Cardiol. 11:613 1965
10. Castellanos, A J Lemberg L Iomnides, G and Salha ek L The vectorcardiogram in right bundle branch block co-existing w th left ventricular focal block Am J Cardiol 18 705 1966
11. Baydar U D Walsh T J and M we, E A vectorcardiographic study of right bundle branch block with the Fra k system *Clinical* correlation in ventricula hypertrophy nd chronic pulmonary disease, Am J Cardiol 18 185 1960.
12. Cabrera, E Garcia-Font R. Gaxiola, A and P leggi, F The vectorcardiogr m of ventricular activation in chronic coronary heart disease, Am. Heart J 55:567 1958
13. Dekker E Buller J and Schu lenburg R M Aid t electrical diagnosis of pacemaker failure Am. Heart J 78 739 1958.
14. Castellanos, A J Mayer J W and Lemberg L The lectrocardiogram and vector cardiogram in W P W associated with bundle branch block Am. J Cardiol 10:657 1962.
15. Castellanos, A. J nd Lemberg L Post infarction onduction disturbances, *in* Hoffman, I editor Vectorcardiography 1965 Amsterdam 1966, North Holland Publishing Co
16. Ca tellanos, A J Centurion M J nd Lemberg L Le ectorcardiogramme dans les blocs bilateraux, Arch. mal oeur 57 71 1964
17. Jones, M A and Feil, H Axis deviation in human bundle branch block, Am. Heart J *36:98, 1948.*
18. Boyardian N and DeChamps, G. Absence of changes of QRS electrical axis with development of intraventricular block Acta cardiol. 9 127 1957
19. Grant, R P Left axis deviation. An lectrocardiographic pathologic correlation study Circulation 14:233 1956.
20. Grant, R P Clinical lectrocardiography New York, 1957 McGraw Hill Book Company Inc.
21. Lihenoff A J Marked left axis deviation Am. J Cardiol. 14:330 1964
22. Corne R A., Parker T W Branderburgn, R O nd Brown, A. L. Peri-infarction block Post myocardial infarction intraventricular conduction disturbance Am. Heart J 69 150 1965.
23. Castle C H and Keane, W J Electrocardiographic peri-infarction block A clinical and pathologic l correlation Circulation 31:403 1965.
24. Pryor R nd Blount, S G The clinical significance of true *left* axis deviation. *Left* ventricular blocks, Am. Heart J 72:391 1966.
25. Schamroth L and Blumsohn, D The sig n ficance of left axis deviation in heart disease of the African, Brit Heart J 23:405 1961
26. Dante, H. D Greenfield, J C and Estes, E H. Left axis deviation, Am J Cardiol. 14:330 1964
27. Spach, M S Boineau J P Long E. C. Gabor H B and Gallie, J M Genesis of the ectorcardiogram (lectrocardiogram) in endocardial cushion defects, Hoffman, I editor Vectorcardiography 1965 Amsterdam 1966, North Holland Publishing Compa y
28. Gra t, R P Tomlinson F B and Van Buren J R Ventricular activation in pre-excitation (W P W) syndrome, Circulation 18:355 1958.
29. Abramson D I Katz, L N Margolin, S and Lourie R Variations in the electrocardiographic form of experimental ventric lar ectopic beat in the monkey and dog Am Heart J *15:217 1937*
30. Nahum L H Hoff H E nd Kaufman, W Configuration of anterior and posterior septal extrasystoles in the standard leads of the electrocardiogr m, Am. J Physiol. 131:198, 1941
31. Scherf D and Schott A Extrasystoles nd allied arrhythmias, New York, 1953, Grune & Stratton, Inc

Spatial QRS curves of the newborn infant

Spatial magnitude, velocity, and orientation (Frank system)

Lorin E. Ainger, M.D., M.Sc.
Memphis, Tenn.

Spatial electrocardiographic curves for velocity, magnitude, and orientation (azimuth and elevation) plotted on the ordinate against actual or normalized time abscissae have been proposed as a complementary method for examination of the spatial electrocardiographic characteristics of orthogonal lead recordings. Spatial curves for adults have been recorded on a continuous time base by analogue computers[1] or by digital computation of magnetic tape electrocardiographic recordings. This method of display has the advantage of preserving time informational content which is often lost in many forms of conventional loop display.

It is the purpose of this report to present spatial QRS curves for magnitude, velocity, and orientation derived from Frank lead recordings from a small group of term normal newborn infants, all recorded on the first day of life. This information was derived from a pilot analysis performed during modification and testing of a digital computer program for analysis of a much larger group of recordings. After the spatial curves were obtained, we became aware of the fact that the literature did not contain any of this information for newborn infants and since the curves were unique in some aspects, it seemed worthwhile to report this work.

Subjects and methods

For the purposes of this study, Frank lead recordings of thirteen normal term infants were selected at random from our magnetic tape library of orthogonal lead electrocardiographic recordings of a large group of normal infants and children. This tape library has been compiled during the course of longitudinal study of a group of normal children from the lower socioeconomic scale who are under continuous medical supervision through enrollment in the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Blindness. None of the study infants had any perinatal cardiorespiratory distress, evidence of heart disease at birth (or on subsequent examination). All have been free of significant anemia and have had normal growth and development during the first year of life.

Details of recording have been published elsewhere. In general, the recording instrumentation consists of three Minneapolis-Honeywell electrocardiographic pre-

From the Section of Pediatric Cardiology, Department of Pediatrics, University of Tennessee College of Medicine, and the City of Memphis Hospitals, 860 Madison Avenue, Memphis, Tenn. 38103.
This work was supported by Grants HE-05718 and HE-09495 from the National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Md.
With the technical assistance of Patrick J. Brignole, B.S., and Bill R. Campbell.
Received for publication March 1967.
Associate Professor and Chairman, Section of Pediatric Cardiology, 860 Madison Avenue, Memphis, Tenn. 38103.

amplifiers operated at a gain of 1,000 simultaneously calibrated so that a millivolt current input results in a 2 cm. deflection of the oscilloscopic beam. Preamplifier input impedance is 20 megohms, frequently response is flat to 5,000 c.p.s. and noise level of the entire system is less than 20 μV with a peak-to-peak range of ± 1.4 mV. The electrocardiographic signal is frequently modulated and recorded at a center frequency of 13.5 K.C. for narrow band magnetic tape recording. X, Y, and Z deflections are recorded simultaneously on ½ inch tape at a speed of 15 inches per second. The tape transport is a Minneapolis-Honeywell LAR 1086 7-channel machine with an IRIG head configuration. All recordings for this study have been made by the same technician. Electrode placement was in the fourth interspace.[7]

The original analogue recordings were converted to digital format on an Airborne Instrument Laboratories A-to-D converter courtesy of Drs. E. Croft Long and Madison S. Spach, Duke University School of Medicine. Digitizing rate was 947 bits per channel per second. The digitized data were formated and then smoothed with a low pass numerical filter.[8,9] Computer recognition of onset and termination of QRS was determined by calculation of QRS spatial velocity curves.[11] Examination of Calcomp plots of these curves obtained by a program through a Programmed Data Processing Unit 7 indicated that a value of 6 μV per second rise time selected as the recognition point[11,12] would identify *onset* and *offset* within ±0.01 msec. of the true time. All data are calculated for display in a left handed Cartesian reference frame as recommended by the American Heart Association Committee for electrocardiography.[4] (Fig. 1). An IBM 1620 digital computer was used for processing and analysis of the data by modification of the digital computational programming procedures described by Pipberger and associates.[3]

Spatial curves for orientation, magnitude, and velocity were plotted as ordinates against a true time abscissa and on a normalized time scale—a procedure proposed by Yano and Pipberger[14] for constructing comparative spatial curves of QRS complexes of varying duration. The QRS is divided into ten equal segments and the spatial values for velocity, magnitude, and orientation are determined at each of the division points. The last two of the ten values were not determined because the wide scatter of values resulting in part from small base-line shifts were considered to introduce too much error. The curve was constructed by connection of the points representing quantitative measurement of the spatial characteristic at that QRS segment.

Since the number of infants in the study was small, no statistical limits were derived other than the arithmetic mean. Spatial

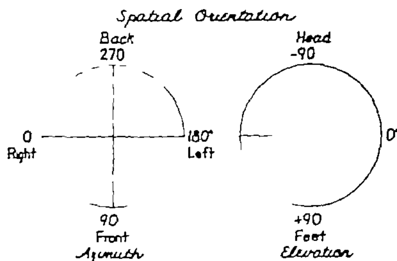


Fig. 1. Reference frame for determination of spatial orientation.

curves were constructed as follows for each normalized or actual time point the arithmetic mean for the group was determined and the curve constructed by connecting the points. The curves superior and inferior to the mean curves were constructed by connection of points representing respectively the highest and lowest values among the thirteen for each of the time intervals. The vertical distance between these points represents therefore the range of observed values for that particular time interval

Results

Spatial magnitude Normalized and actual time base QRS spatial magnitude curves for newborn infants (Fig 2) are quite similar Maximum mean spatial magnitude occurs at the fourth QRS time point corresponding approximately to 0 02 seconds in actual time. In the normalized time curve a second peak mean spatial magnitude occurred at the sixth QRS time point, a point occurring just before 0 04 seconds actual time, and not represented in the actual time curve which does not show this second peak. Actual time base magnitude curves of individual infants frequently show this double maximum spatial magnitude peak The first maximum corresponds to the rightward maximum spatial vector (RMSV) the second corresponds to the leftward maxi-

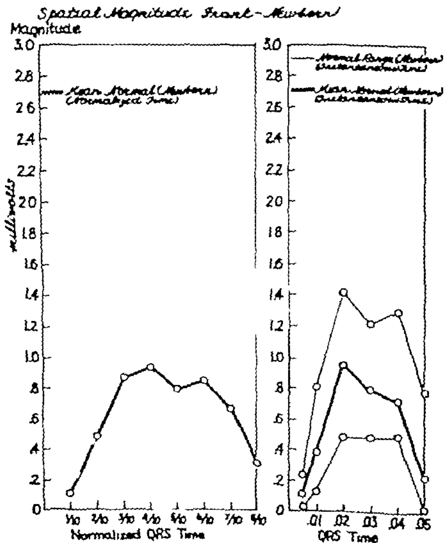


Fig 2 Spatial magnitude of QRS for normal newborn infants

mum spatial vector (LMSV). These vectors are almost equal in magnitude at this age.

Spatial velocity Maximum mean spatial velocity is observed at the mid point of ventricular depolarization (Fig 3) corresponding in time to transfer of force dominance from right to left ventricular activation fronts. Peak spatial velocity occurs earlier in the course of ventricular depolarization in the adult.[14]

Spatial orientation The azimuth mean curve presented in (Fig 4) should be interpreted only in regard to contour between the 1/10 and 6/10 and 0 01 to 0 04 time points since the mean was derived from a heterogeneous loop population (clockwise and counterclockwise inscription—open anterior and posterior crossovers) Too much significance should not be attached to the individual mean values, which were used only to approximate the curve in this case.

It is probably more helpful to visualize the mean not as a line but as a band extending 45 degrees on either side of the mean The great range of values for the initial and terminal points of the curve merely illustrate the great variability of vector orientation encountered in this age group In the time ranges defined above the curve contour is very similar to that presented by Pipberger[4] for right ven

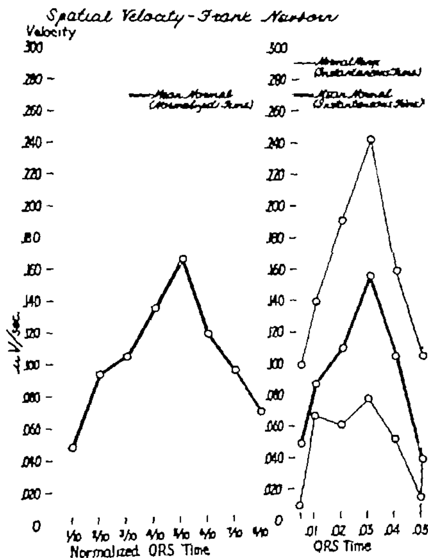


Fig 3 QRS spatial velocity of newborn inf ts

tricular hypertrophy in the adult—left anterior and then right posterior rotation.

Discussion

Although recording performance of the Frank lead network[1] (or any lead network) only approximates orthogonality and orthonormality the approximation is probably close enough to justify mathematical quantitation of the spatial characteristics of the electrocardiogram for newborn infant spatial curve display In general spatial characteristics can be described in terms of the following spatial magnitude spatial velocity spatial orientation, spatial rotation and the spatial orientation and symmetry of the QRS loop

Spatial magnitude is not determined only by the inherent generator characteristics of the heart but also by the recording characteristics of the lead network body size, heart size in relationship to the chest cavity tissue conductivity electrode proximity and other as yet unidentified factors. If all these modifying factors were constant and only a single activation front were present in the myocardium at a specific point in time, spatial magnitude would vary in direct proportion to the surface area of the front. At any given time during the sequence of ventricular activation there are numerous wave fronts of varying size and orientation Spatial magnitude is determined by vectorial summation of all additive and cancellation forces. The relative contribution of the

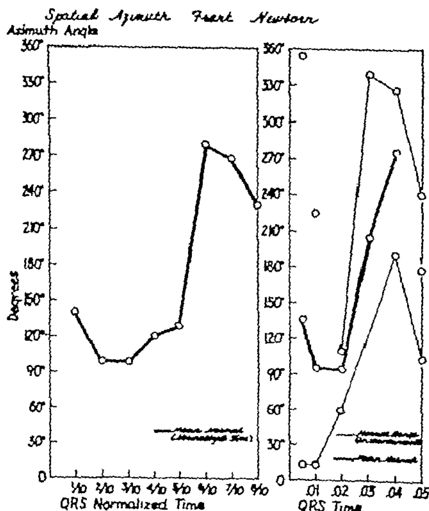


Fig. 4. QRS spatial elevation of newborn infants.

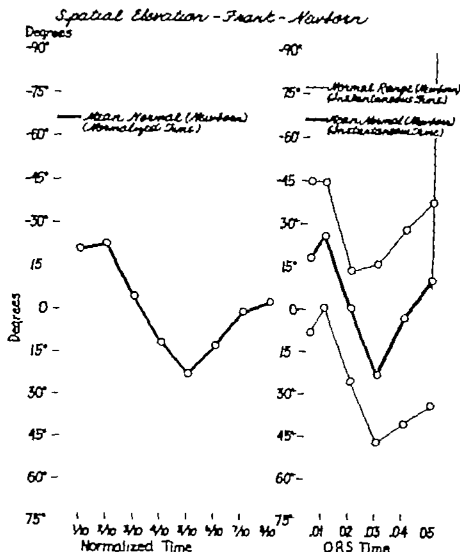


Fig 5 Infant QRS spatial azim th

dipole-moment of the infant heart to spatial magnitude recorded from the sur face cannot be assessed although preliminary work suggests that the dipole-moment of the heart may increase with age.[14] In addition the tendency of the new born infant s loop to lie in a plane (usually in the sagittal but occasionally in the horizontal plane) suggests activation sym metry—balanced wave fronts approximately of equal magnitude advancing in opposite directions through the myocar dium This activation symmetry also would tend to decrease spatial magnitude through force decancellation

Spatial velocity is a measure determined by spatial shifts of the centroid of activation but the absolute value for this measure is partially dependent upon spatial magnitude. Low velocities are associated with wave front advance in a uniform di rection and peak velocities occur when waning dominance of one activation cen troid is superseded by an emergent one. As in the adult the maximum spatial velocity in the newborn infant is observed at the time of shift in the dominant acti vation centroid from the right to the left ventricle. This shift of activation domi nance in the infant does not occur until the midpoint of ventricular activation.

The time course of directional spatial depolarization forces is defined by the spatial curves of the azimuth and elevation

angles (Fig 5) The spatial elevation curve of the newborn infant varies from that of the adult only in a slightly more superior orientation along the ordinate. The azimuth curve is unusual in that the hypothetical loop is characterized by an anterior and leftward rotation with a right and posterior rotation, followed by rotation to the left. Horizontal loops in newborn infants frequently have an initial rightward vector recorded before the 1 10 time point in QRS. This curve for spatial azimuth was almost identical in contour to one presented by Pipberger as characteristic of right ventricular hypertrophy

It is apparent that vector orientations in normal newborn infants show even greater scatter than those recorded later in life—in fact, variability of QRS forces seems to be an integral characteristic of this age group For example the 0 005 seconds azimuth vector orientation values for the individuals were 263 114 81 64 111 45 180 12 100 117 353 86 and 252 degrees. This variation can be explained in part, by direction of loop inscription the orientation of the planar loop in its respective plane and the configuration of the loop whether open and oval a long and narrow figure-of-eight etc. If the initial vectors are disregarded, the individual spatial curves approximate the mean curve contour rather well in spite of this individual variation. Shifting the individual curve one time point to the right or left often improves this agreement with the mean curve

Summary

Spatial curves, derived by digital computational procedures from Frank lead system recordings on the first day of life in thirteen term newborn infants have been presented. Although these data are not considered definitive they do illustrate some interesting aspects of the spatial characteristics of electrocardiograms recorded at this age and the curves reflect the unique anatomic characteristics of the heart for this period of life. Of interest also is the great normal variability in time course of force orientation characteristic of this age.

REFERENCES

1 Sayers, B. McA., Silberberg F G and Duke, D F Electrocardiographic spatial magnitude curve in man, Am. Heart J 49:323 1955
2. Abildskov J A., Ingerson, W E. and Hisey B. L. Linear time scale for spatial vectorcardiographic data, Circulation 14:556, 1956
3. Moore, A D Harding P and Dower G. E. Polarcardiograph. An analogue computer that provides spherical polar coordinates of the heart vector Am. Heart J 64:382, 1962.
4. Pipberger H. V Use of computers in interpretation of electrocardiograms, Circulation Res. 11:555, 1962.
5 Yano, K., and Pipberger H V Spatial magnitude orientation and velocity of the normal and abnormal QRS complex, Circulation 29 107 1964.
6. Ainger L. E. Vectorcardiographic studies in infants and children. I Comparative orthogonal lead studies in the neonatal period, Am J Dis. Cardiol. In press.
7 Hugenholtz, P G. and Liebman, J The orthogonal vectorcardiogram in 100 normal children recorded by the cube system Circulation 26:891 1962.
8 Ander E B An error bound for a numerical filtering technique J A Computing Mach. 12 137 1965
9 Technical information series Document No. 575D340, Missile and Ordinance Systems Department, General Electric Co. Chapter 4 May 1957
10 Fullenweider E. D and McNamee, B J Filtered sample functions, U S. Naval Ordinance Laboratory Tech Mem No. 64-104 Corona, California, 1965
11 Pipberger H V Stallmann F W Yano, K. and Draper H W Digital computer analysis of the normal and abnormal electrocardiogram Progr Cardiovas. Dis 5:378, 1963
12. Blomqvist, G The Frank lead exercise electrocardiogram, Acta med scandinav Suppl 440 178, 1965
13 Stallmann, F W and Pipberger H V Automatic recognition of electrocardiographic waves by digital computer Circulation Res 9 1138 1961
14. Committee on Electrocardiography American Heart Association. Circulation 10:564, 1954
15 Yano, K., and Pipberger H V Spatial magnitude, orientation, and velocity of the normal and abnormal QRS complex, Circulation 29 107 1964
16 Pipberger H. V and Lilienfield, L S Application of corrected electrocardiographic lead system in man, Am J Med 25:539 1958
17 Gamboa, R., and Gersony W M The applicability of the Frank lead system in infants and children, Pediatrics 28:585 1966.
18. Ellison, R. C Fischmann, E. J and Hugenholtz, P G. Evidence for progressive increase in the heart' electromotive forces with body growth Circulation 34:III—96 Suppl. 4 1966

Mechanical injury to the coronary arteries during operative cannulation

Noel H. Fishman, M.D.
J. E. Youker, M.D.
Benson B. Roe, M.D.
San Francisco, Calif.

Continuous perfusion of both coronary arteries with indwelling cannulae has been recommended for preservation of myocardial integrity during operations upon the aortic valve. The importance of this technique was emphasized by Mc-Goon and co-workers[1] in reporting their impressive series of successful prosthetic valve replacement operations.

Although Sanger and associates[2] cautioned that poorly fitting cannulae and circumferential sutures could injure the coronary arteries, only one case had been reported in which intimal trauma was identified on pathologic examination. We shall describe ten operative deaths in which cannulation induced injury was the responsible factor. In only two of these was the correct diagnosis made prior to autopsy.

The charts, operative reports, and autopsy findings of eighteen patients who died immediately after operations performed between January 1, 1965, and December 1966 were reviewed to determine the incidence of fatal coronary artery injuries. Operative reports were searched for evidence of a difficult cannulation, noticeable trauma, and visible areas of infarcted or ischemic ventricular myocardium. The bypass records were examined to document sudden irreversible changes in the flow characteristics during coronary artery perfusion. The pathologic findings were correlated with the clinical observations and postmortem coronary angiography was performed in five cases (Table I).

Materials and methods

In all patients extracorporeal circulation was maintained with a disposable bubble oxygenator* primed with a balanced electrolyte solution that contained 4 Gm. per cent albumin. Flow rates ranged from 2.2 to 3.1 L. per minute at temperatures of 23 to 26° C. The type of indwelling coronary perfusion catheter used in each case was determined by the anatomic configuration of the ostium and proximal coronary artery. Four different types of cannulae were used: Latex-covered expanding metal tip, Silastic bulb-tip,* O ring, and self inflating (Fig. 1).

A separate coronary perfusion system was used consisting of a closed reservoir filled by a calibrated roller pump. The pressure which was continuously moni-

From the Department of Surgery (Drs. Fishman and Roe) and Radiology (Dr. Youker) of the University of California School of Medicine, San Francisco, Calif.
Received for publication March 22, 1967.
*Travenol Laboratories, Morton Grove, Ill.



Fig. 1. Coronary perfusion cannulae. A, Rigid latex-covered expanding metal tip (Roe). B, bulb-tipped plastic (Spencer-Malette). C, Self inflating balloon-tip (King). D, "O" ring (Bosher).

tored was kept below 100 mm. Hg and the total flow never exceeded 200 ml. per minute. Both perfusion lines were connected to the common pressure source providing automatic decompression in the event of obstruction to flow in one cannula. The perfusion pressure and line resistance were continuously monitored by a Sanborn oscillograph and a direct writer.

Postmortem radiologic examination

Postmortem coronary angiography was performed by the following technique. Immediately after the heart was removed from the body, Micropaque contrast material was slowly injected into the root of the clamped aorta until the smaller branches were adequately filled. Radiographs were obtained with the heart held in several positions (300 MA, 3 seconds at 56 KVP with a tube film distance of 40 inches). Superimposition of the coronary arteries was reduced to a minimum in the left anterior oblique projection. The small amount of barium which occasionally leaked through the valve prosthesis into the left ventricular cavity did not create a diagnostic problem.

Case reports

Case 1. A 64-year-old woman had functional class IV disability on the basis of severe congestive failure, angina decubitus, and syncope. A peak systolic gradient of 160 mm. Hg was demonstrated across the aortic valve.

At operation on January 21, 1965, a heavily calcified bicuspid valve was excised and was replaced with a Starr-Edwards prosthesis. The left coronary artery was easily cannulated with an expanding-tip cannula. Initial attempts to cannulate the right coronary artery were unsuccessful, but after gentle dilation of the ostium with a clamp a self inflating cannula was successfully introduced. However, the artery would accept no flow from this catheter. Although there was satisfactory left ventricular output when the aorta was first unclamped, recurrent intractable ventricular fibrillation ensued secondary to an irritable focus on the anterior surface of the right ventricle.

An autopsy showed extensive ecchymosis on the anterior surface of the heart. A hole 3 mm. in diameter was found in the right coronary artery near its origin which corresponded in position to an irregular laceration of the intima. Focal hemorrhage and leukocyte infiltration were seen in this area during microscopic examination.

Case 2. A 51-year-old woman who had had acute rheumatic fever was in functional class IV because of cachexia and refractory congestive failure secondary to severe aortic stenosis. A mean left atrial pressure of 27 mm. Hg and severe pulmonary hypertension were noted during cardiac catheterization which could not be completed because the patient developed pulmonary edema.

At operation on November 24, 1965, a bicuspid aortic valve with nodular calcifications was excised. An expanding-tip coronary perfusion cannula was inserted into the left coronary ostium without incident. When a balloon-tipped cannula was inserted into the right coronary ostium, however, the artery avulsed from the aorta. After reanastomosis, no further perfusion of this artery was attempted. When the Starr-Edwards prosthesis had been implanted, an intimal tear was found in the left coronary artery. Since this could not be successfully repaired, the intimal flap was excised. Aortic closure could not be accomplished because the tissue was too friable to support sutures.

Autopsy showed a frank hematoma along the course of both coronary arteries and dissection of the media of the left coronary artery was seen on microscopic study.

Case 3. A 65-year-old man had recurrent syncope. Sclerotic coronary arteries were demonstrated by angiography. The peak systolic gradient across the aortic valve was 72 mm. Hg.

At operation on November 3, 1965, the coronary arteries were palpably calcified. A tricuspid calcified aortic valve was excised and was replaced with a Roe-Moore leaflet prosthesis. Seemingly satisfactory bilateral coronary perfusion was obtained by using expanding-tip cannulae. However, after the aorta was closed, the heart was unable to support the circulation without extracorporeal assistance, and progressive ventricular irritability ensued.

An autopsy showed early branching of the left coronary artery within 4 mm. of the ostium. Multiple large intimal plaques were present along the entire artery, reducing the intimal diameter to less than 1 mm. at several points. No holes were noted by the pathologist, but epicardial hemorrhage surrounded the anterior descending branch of the left coronary artery and infiltration of scattered acute inflammatory cells was seen on microscopic

Table I Pathologic and angiographic findings after mechanical injury to the coronary arteries

Case	Ca he sed	Complic tion	Condition fter bypass	P thologic find g	A giographic find gs
1	Right self inflating catheter following dilatation of small orifice	N flow after insertion	Refractory entricular fibrillation	Hemorrhage over tenor myocardium. Hole in right coronary artery 1.5 cm from ostium Lacerated intima	Not performed
2	Right self-inflating type left expanding tip	Artery led I tima torn	Aorta could not be loed successfull	Hematoma around both coronary arteries and dissection in th left coronary artery	Not performed
3	Left expanding metal tip	None	Could not sustain the circulation without pump assistance	Epicardial hemorrhage long course of anterior descending coronary artery I flammatory cells were seen	Not performed
4	Right self-inflating catheter with ret in ing suture	None	Good, but followed by sudden deterioration nd death 36 hours postoperat ely	I timal flap with recent central thrombus	Not performed
5	Left bulb-tipped in patulous ostium	I timal laceration repaired	Inadequate contraction of left ventricle	N intimal damage noted in report. Ecchymosis around left coronary artery	Not performed

6	Left unknow type	None	Inadequat contraction of left entricle	Ecchymosis around left coronary artery Subendocardial ecchy moses. N holes seen on pathologic examination	External compression nd partial occlusion of proximal left coronary artery
7	Left expanding tip annuls	Flow stopped suddenly h le trium as being ret acted	Poor left entric lar contraction Died 12 hours postoperatively	Clotted blood in left trio-entricular sulcus. I timal laceration l left coronary artery I terstitial hemorrhage and loss of triations l muscle cells	Dissection of left coronary artery and extra asation of ontrast material int inter trial septum
8	Left bulb-tipped and self-l flating catheters	Had t be reinserted several times	Coordinated rhythm could not be mai tained	Pathologic report widel patent coronary arteries	External compression of left oronary artery
9	Left self-inflating type after ostial dilatation	N flow after insertion	Refractory fibrillation of left entricle	Hemorrhage around anterior descending and circumflex coronary arteries. T o separate left oronary ostia Immediat branchi g of right coronary artery	Dissection of anterior descend g oronary artery along it entire length
10	Right coronary artery could not be can lated	—	Inadequ t cardiac output. Died 1 hou postoperati el	Severe theromata t base of aorta. Right coronary ostium was difficult to see	Almost absent filli g of right coronary artery

examination A barium injection tudy was not performed.

Case 4 A 36-year-old woma had a 2½ year history of illness, which began with transient left hemiparesis and chest pain followed by progressive exertional dyspnea, palpitations, nd paroxysmal nocturnal dyspnea (class III)

On September 22 1965 the aortic valve was replaced with a Roe-Moore tricuspid prosthesis, and a Starr Edwards prosthesis was nserted in the mitral area. Uneventf l bilateral coronary artery perfusion was achieved with self-inflating ca ulae which were held in place with lateral sutures of fine silk. After doing well for 24 hours he had a myocardial infarction, nodal arrhythmias, and left hemiparesis in rapid succession and died 12 hours later

Postmortem examination showed that the right coronary artery was occluded by fresh thrombus which had formed on flap of detached intima. The temporary suture which was used to retain the cannula in place during the operation was established as the origin of this flap. Ecchymosis was also seen around the right coronary artery A barium injection study was not performed.

Case 5 A 72 year-old man had congestive failure angina and several ttacks of near syncope (class III).

At operation on J nuary 21 1965 a stenotic bicuspid calcified valve was replaced with large Starr Edwards prosthesis The left coronary ostium was so large that the largest bulb-tipped cannula could not be maintained in place even with purse-*tring suture, and had to be replaced with a large* expanding-tip cannula. At tumal tear was sutured. Effective left ventricular contraction could not be obtained despit the fact that the aorta as re-opened and further efforts were made to repair the laceration

The autopsy report indicated that the coronary arteries were widely patent. A large hematoma was seen round the left coronary artery and may ha e interfered with flow although no definite obstruc tion was demonstrated The i timal laceration was not mentioned in the pathologist report. Barium injection was not performed

Case 6 A 65-year-old woma had constant n-gina pectoris and had had three episodes of exer tional syncope each followed by several hours of nconsciousness. She had no symptoms of congestive *heart failure Murmurs typical of aortic stenosis* and insufficiency were noted The peak systolic gradient across the aortic alve was 106 mm Hg

O January 28 1966 a bicuspid calcified aortic valve was removed and replaced with small Cutter Smeloff prosthesis. Both coronary arteries were perfused w thout apparent incident. The heart beat well on bypass but the contractile force was not adequat t sustai the circulation w thout the assistance of the heart-l ng machine.

At topsy ecchymoses were found long the course of the prox mal left coronary artery There were extensive subendocardial ecchymoses nd extravasation of i jected graphic contrast material into the interatrial septum but no com m nication with major vessel could be established t that poi t Compression nd partial occlusion of the proximal left coronary artery could be demonstrated on the postmortem angiograms (Fig 2)

Case 7 A 45-year-old man with combined calcific *ortic nd mitral stenosis had had closed mitral* commissurotomy 1956 followed by restenosis of the mitral alv and severe pulmonary hyper tension Two years before the present admission he had transient left hemiparesis.

At operation on March 17 1965 heavily calcified mitral and aortic val es were eplaced with Starr Edwards prostheses. After the aortic alve was excised, expanding tip coronary perfusion cannula were introd ced. During exposure of the mitral valve, which required firm retraction because of posterior adhesions, resistance in the coronary per fusion line rose sharply nd flow could not be reinstituted by changing the position of the ca nula. Following the proced re th left entricl did not contract well. Th lectrocardiogram showed obvious left entricular infarction and the patient died 12 hours after the operation

On postmortem examination the left ventricular wall was soft Clotted blood and ecchymoses were seen around the left triov entricular junction. The right coronary artery was open, but was partially occluded by therosclerosis The left coronary circumflex coronary artery had an i timal tear l lt 1.5 cm. from the osti m. Microbarium suspen sion which had been injected i to the aorta, was seen subi timally for a distance of 2.0 cm. beyond th laceration Microscopic examination showed recent i terstitial hemorrhages nd left entricular infarction with loss of striation

Case 8 A 42-year-old oma with history of rheumatic fever had f nctional class IV cardiac disease on the basis of i tractable left entricular failure resulting from combined aortic nd mitral



Fig 2 I jection of barium bove the ortic prosthesis shows irregular narrowing of left coronary artery due t external pressure (arrow).

valve disease. She had had myocardial infarction six years previously.

The aortic and mitral valves were replaced on December 16 1965 with Cutter Smeloff prostheses. Prior to the institution of cardiopulmonary bypass, she developed bradycardia and hypotension. The coronary arteries were cannulated easily. Although both self-inflating and bulbed-tipped catheters were employed the left coronary cannula was repeatedly expelled and had to be reinserted. Following the procedure coordinated rhythm with adequate contraction could not be maintained, and after 83 D.C. shocks, the heart could no longer be defibrillated.

At autopsy the coronary arteries seemed to be widely patent. However contrast studies performed prior to gross examination showed external compression of the left coronary circumflex artery by soft tissue mass, presumably hematoma.

Case 9. A 56-year-old man with combined aortic stenosis and insufficiency had recurrent angina, pulmonary edema and dyspnea on exertion (class III). The peak systolic left ventricular-aortic pressure difference was 100 mm. Hg.

At operation on May 10 1966, a bicuspid, calcified aortic valve was replaced with a Cutter Smeloff prosthesis. There were two small left coronary ostia. One was cannulated after great difficulty but would accept no flow. The right coronary artery was easily cannulated. After the aorta was closed and the patient rewarmed, the left ventricle could not be defibrillated even though the right ventricle spontaneously defibrillated and beat well.

At autopsy the right coronary artery was seen to bifurcate within 3 mm. of its origin. The left coronary circumflex and anterior descending arteries had separate aortic ostia. Hemorrhage was present at the origin of both left coronary arteries, which collapsed under pressure. Although no area of internal dissection was described on the pathologist report, dissection of the left anterior descending artery could be seen extending to the tip of the left ventricle on the postmortem angiogram (Fig. 3).

Case 10. A 65-year-old man had angina and syncope. Selective coronary angiograms demonstrated diffuse and extensive coronary artery atherosclerosis. The classic physical signs of severe aortic stenosis were present. There was a 100 mm. Hg peak systolic gradient across the aortic valve.

At operation on June 14 1966 a Cutter Smeloff prosthesis was implanted to replace a calcified bicuspid aortic valve. During the operation, several unsuccessful attempts were made to cannulate the right coronary ostium. The patient died one hour after operation from heart block and low output.

Autopsy showed extensive coronary artery disease, including several severe constrictions along the course of each artery. There was a large old left ventricular infarct. No evidence of coronary dissection was seen. The right coronary ostium was difficult to identify because of overlying thick aortic



Fig. 3A. Case 9. The fine radiolucent line (arrow) identifies dissection in the main left coronary artery and the entire anterior descending branch.



Fig. 3B. Case 9. The extent of the dissection in this patient is best seen on another view with the heart open and the prosthesis removed.

theromata. The postmortem supra 1 ula barium injection showed absence of filling of the right coronary arteries.

Discussion

During a two-year period 144 patients had valve replacement operations at the University of California Medical Center 24 of these were multiple replacement operations and 17 patients had an additional valve reconstructed Of the 73 patients in whom the aortic valve was replaced 18 died (mortality rate 25 per cent) The mortality rate in the remaining 71 patients was only 3 per cent Coronary artery damage was confirmed in 10 patients by postmortem evaluation Gross evidence of infarction ecchymosis, or hemorrhage was found in 6 patients, and focal inflammation was seen microscopically in 3 Increased coronary perfusion pressure associated with a decreased flow rate occurred during operation in 4 patients. Arterial dissection or compression was demonstrated in 5 patients by postmortem angiography (Table I)

The desirable objective of maintaining uninterrupted coronary perfusion during aortic valve surgery is clearly difficult to accomplish in some patients and currently available perfusion techniques are potentially dangerous. The coronary ostia are often diminutive patulous, or multiple Cannulae often cannot be maintained in position without excessive manipulation, replacement or circumferential suturing A catheter inserted into an artery which branches early may exclude a portion of the vascular bed from the perfusion Atherosclerotic plaques are known to act as a point of dissection in other arteries and the proximal coronary arteries are often sclerotic in patients with acquired valvular heart disease Cooley[4] and Sanger[3] have abandoned coronary perfusion altogether

Subepicardial petechiae have been noted frequently after coronary perfusion even though the line pressure in the coronary perfusion reservoirs is kept below 100 mm Hg and the left atrium is decompressed. When the high resistance in the long perfusion lines and narrow cannulae is taken into account an even smaller pressure is present in the coronary arteries. These small hemorrhages therefore may be due to loss of intrinsic control of arteriolar resistance in the nonbeating heart resulting in an unusually high capillary pressure. It is possible that the operative deaths which have been previously attributed to obscure causes such as the low output syndrome or small ventricular cavity may in fact have been caused by trauma to coronary arteries with resultant obstruction to flow Evidence of intimal dissection is often overlooked on routine examination where attention is paid mostly to thrombotic occlusion In Case 9 the extensive medial dissection seen on the postmortem angiogram was not appreciated on gross examination In Case 5 the area in which the intima was resected and sutured was not reported on the pathologic examination The proximal left coronary artery is especially difficult to examine by the standard autopsy procedure.

All self retaining cannulae are designed on the principle that the ostium is the narrowest point in the proximal coronary artery An enlargement at the tip tends to prevent the otherwise unavoidable extrusion of the catheter by back pressure (Fig 3)

Although the expanding metal tip cannula can be inserted without dilating the ostium the metal arm of this cannula is relatively long and inflexible

The bulb-tipped catheters have a relatively sharp point and the bulb even though elastic may produce ostial laceration and plaque disruption

The O ring cannula must like the bulb tip be popped in but it is more easily deformed during insertion

The advantage of the balloon (self inflating) catheter described by Kang is that the pressure in the balloon can never exceed the perfusion pressure Dilatation of the ostium by this catheter is minimal The disadvantage of this catheter lies in the long balloon length which may obstruct flow to an early branch of the coronary artery

As a result of this experience we no longer routinely perform bilateral continuous coronary artery perfusion The rigid expanding tip and the bulb-tipped cannulae have been abandoned and attempts to insert the balloon-tipped cath

eter are restricted to the gentlest possible effort. Otherwise unilateral or intermittent perfusion combined with hypothermia has been used and occasionally perfusion has not been possible at all. In these instances satisfactory ventricular performance has been achieved and no further coronary artery damage has occurred

Summary

An extensive review of 18 patients who died after aortic valve surgery indicated that operative cannulation caused fatal mechanical injury in 10 of these patients. Underlying coronary arterial anomalies and atherosclerosis were present in most of these cases. It is probable that many operative deaths which have formerly been attributed to the patient's heart disease are really due to iatrogenic coronary artery obstruction

Diseased coronary arteries and the technical problems of cannulation present hazards which may offset those of intermittent ischemia.

REFERENCES

1 McGoon, D C., Pertana, C., and Moffitt, E. A. Decreased risk of aortic valve surgery Arch. Surg 91 779 1965
2. Sanger P W Robicsek F., Daugherty H. K., Gallucci, V and Lesage M A. Topical cardiac hypothermia in lieu of coronary perfusion. J Thoracic & Cardiovas. Surg 52:533 1966.
3. Hellbrunn, A., and Zimmerman, J M) Coronary artery dissection a complication of cannulation J Thoracic & Cardiovas. Surg 49 767 1965.
4. Roe, B. B., Hutchinson, J C., and Swenson, E. E. High-flow body perfusion with calculated hemodilution Ann. Thoracic Surg 1:581 1965
5 Roe B. B. and McKay L. M An improved watertight coronary cannula J Thoracic & Cardiovas. Surg 43 139 1962.
6. Spencer F C and Malette W Dow Corning Bulletin, May 1965
7 King B J An improved coronary artery perfusion cannula, J Thoracic & Cardiovas. Surg 45:667 1963.
8. Bloodwell, R. D Gill S. S Pereyo, J A., Hallman, G L., De Bakey M E., and Cooley D A Cardiac valve replacement without coronary perfusion, Circulation Suppl. III p 58, (Oct.) 1966.

The congenital cardiovascular anomalies underlying reversed coarctation*

Elliot Chesler, M.B., M.R.C.P. (Edin.)
James H. Moller, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

The term reversed coarctation has been applied to the situation wherein the blood pressure is higher in the lower than in the upper limbs, a phenomenon which is the reverse of the findings observed in classical coarctation of the aorta. In the adult this phenomenon, which has also been called "pulseless disease"[1] or "aortic arch syndrome," is almost always the result of acquired disease. Syphilitic or nonspecific aortitis, dissecting aneurysm of the aorta, and peculiarly localized atherosclerosis are among the conditions that may be responsible for acquired forms of reversed coarctation.

The possibility also exists that congenital anomalies may be responsible for reversed coarctation. While there is little in the way of documentation of blood pressure readings among such cases, it is appropriate to review those anatomic states which appear to cause reversed coarctation on a congenital basis. Through an awareness of these states, interest may be stimulated in the clinical aspects of the problem and may aid in understanding the phenomenon when observed.

In contrast to the acquired forms of disease encountered in adults, the congenital anomalies which underlie reversed coarctation are seen predominantly in infancy, since with few exceptions the combination of anomalies present are usually responsible for death before childhood is reached. Reversed coarctation caused by congenital anomalies usually is a manifestation of a condition in which the brachiocephalic arteries arise from a low pressured aortic compartment from which a barrier to a higher pressured distal aortic compartment is present. Segmentation of the aorta into two pressure compartments will occur when three conditions are fulfilled as follows: (1) the aorta is supplied totally or partially by the right ventricle through a patent ductus arteriosus, (2) an obstruction in the aortic arch is situated proximal to the ductus and (3) an obstruction is present in the pathway to the ascending aorta. Reversed coarctation may also occur, however, in association with supravalvular aortic stenosis when the ostia of the branchiocephalic vessels are stenotic.

The anomalies of the aorta which cause reversed coarctation are classified in Table

From the Department of Pathology, The Charles T. Miller Hospital, St. Paul, Minn. and the Departments of Medicine, Pediatrics and Pathology, University of Minnesota, Minneapolis, Minn.
This study was supported by Public Health Service Research Grant 5 RO1 HE-05694 and Research Training Grant 5 T1 HE 5570, from the National Heart Institute.
Received for publication March 27, 1967.
*Department of Pathology, The Charles T. Miller Hospital, 125 West College Avenue, St. Paul, Minn. 55102.

Table I Classification of congenital causes of reversed coarctation

- I Aorta supplied in toto or in part by the right ventricle through patent ductus arteriosus
  - A. Coarctation proximal to a patent ductus
    - 1 Aorta supplied entirely by the right ventricle
      - a Aortic atresia
      - b. Aortic and mitral atresia
    - 2 Aorta supplied predominantly by the right ventricle
      - a. Mitral atresia and patent but hypoplastic aortic valve and ventricular septal defect
      - b. Aortic stenosis with hypoplastic left ventricle
  - B Interruption or atresia of the aortic arch with subaortic stenosis and ventricular septal defect
- II Aorta supplied entirely by the left ventricle
  - A. Stenosis of branches of arch in association with supra valvular aortic stenosis

I In some cases the obstruction takes the form of classical coarctation, in others interruption of the aortic arch In one situation there is obstruction of the ascending aorta (supravalvular aortic stenosis)

The purpose of this communication is to survey those anomalous anatomic patterns which may be responsible for these phenomena and to present illustrative cases of the various anatomic patterns. The material for this study is drawn from the files of the Cardiovascular Registry of The Charles T Miller Hospital

Aorta supplied in toto or in part by the right ventricle through a patent ductus arteriosus

Coarctation proximal to a patent ductus In the presence of coexistent aortic and mitral atresia aortic atresia and certain forms of aortic stenosis or mitral atresia, varying degrees of hypoplasia of the left sided cardiac chambers are present. Under these circumstances the aorta is supplied totally or partially by the right ventricle through a patent ductus arteriosus and the ascending aorta is perfused in a retrograde fashion. A coarctation of the aorta situated proximal to the ductus will therefore obstruct the blood supply to the head and upper limbs and result in reversed coarctation.

AORTA SUPPLIED ENTIRELY BY THE RIGHT VENTRICLE. When the aortic valve alone is atretic (Fig 1 *A*) or when there is coexistent aortic and mitral atresia (Fig 1 *B*) blood from the left side of the heart escapes into the right atrium through a herniation of the foramen ovale or an atrial septal defect. This mixed blood is ejected from the right ventricle into the pulmonary trunk and into the aorta by way of the ductus arteriosus.[4] The pressure in the ascending aorta is thus dependent on the severity of the coarctation proximal to the ductus.

Aortic atresia The specimen illustrating aortic valvular atresia was obtained from a male infant six weeks of age (Fig 2 *A*) The ascending aorta was markedly hypoplastic and measured 1 mm in luminal diameter The pulmonary trunk was markedly dilated and the ductus connected with the descending aorta. A coarctation was present proximal to the ductus, and the left subclavian artery originated distal to the ductus. In this case therefore the reversed coarctation syndrome would be incomplete because the left arm would have a higher pressure than the right. In most instances of aortic atresia with coarctation, the left subclavian artery arises proximal to the coarctation

Aortic and mitral atresia An illustrative case of coexistent aortic and mitral atresia is that of a male infant two months old (Fig 2 *B*) The blood pressure in the right arm and right leg were each recorded as 75 mm measured consecutively by the flush technique. In the pathologic specimen a left ventricle could not be identified macroscopically and both mitral and aortic valves were atretic. The only outlet for the left atrium was an atrial septal defect. The ascending aorta was hypoplastic measuring 3 mm in diameter in contrast to the greater width of the pulmonary trunk and descending aorta, which measured 12 and 9 mm. respectively Immediately distal to the left subclavian artery and proximal to the ductus was a coarctation of the aorta.

AORTA SUPPLIED PREDOMINANTLY BY THE RIGHT VENTRICLE. In this group there is patency but varying degrees of hypoplasia of the ascending aorta the aortic valve, and left ventricle. In mitral atresia, if the left

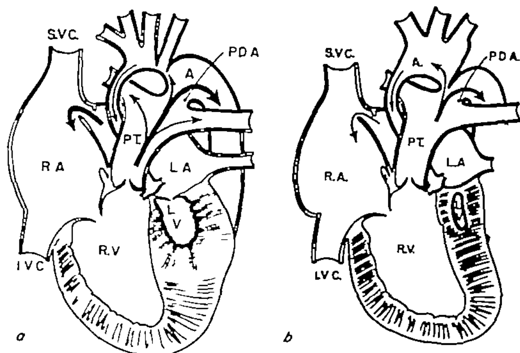


Fig. 1. *A*, Diagrammatic representation of central circulation in aortic atresia with coarctation of aorta proximal to patent ductus arteriosus. In this and in succeeding illustrations, *R.A.* = right atrium, *L.A.* = left atrium, *L.V.* = left ventricle, *P.T.* = pulmonary trunk, *A* = aorta, *I.V.C.* = inferior vena cava, *S.V.C.* = superior vena cava, *P.D.A.* = patent ductus arteriosus. *B*, Diagrammatic representation of central circulation in aortic and mitral atresia with coarctation of aorta proximal to patent ductus arteriosus.

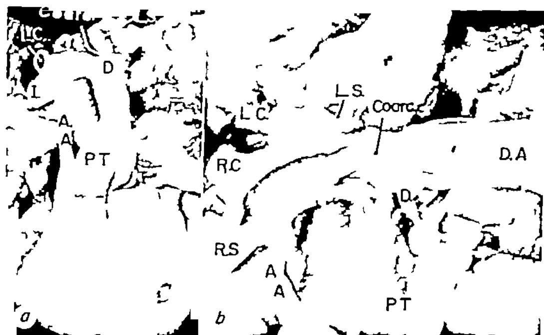


Fig. 2. *A*, Specimen of heart and great vessels from a male infant six weeks old with aortic atresia showing the hypoplastic ascending aorta (*A.A.*), enlarged pulmonary trunk and coarctation of the aorta (*Coarc.*) proximal to the patent ductus arteriosus (*D.*). The left subclavian artery (*L.S.*) arises distal to the coarctation. *B*, Specimen of the great vessels from a male infant two months old with aortic and mitral atresia showing a coarctation proximal to the patent ductus and the hypoplastic ascending aorta. *L.C.* = left common carotid artery, *R.S.* = right subclavian artery, *L.S.* = left subclavian artery.

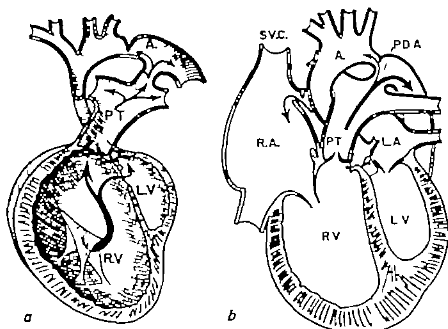


Fig. 3. A Diagrammatic representation of the central circulation in mitral atresia with coarctation of the aorta proximal to patent ductus arteriosus. B Diagrammatic representation of the central circulation in severe congenital unicuspid aortic valvular stenosis with coarctation of the aorta proximal to patent ductus arteriosus.

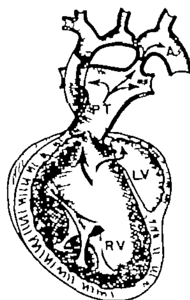


Fig. 4. Diagram of the heart and great vessels in a case of mitral atresia from an infant three days old. The arch of the aorta is hypoplastic in the segment between the innominate artery and the ductus arteriosus. A coarctation of the aorta is present proximal to the ductus and the left subclavian artery arises distal to the coarctation.

ventricle and aorta are well developed in the presence of a large ventricular septal defect, right ventricular blood may enter the ascending aorta via the left ventricle. Similarly in mild aortic stenosis the left ventricle and aorta are not hypoplastic and the ascending aorta may be supplied entirely by the left ventricle. If the contribution made by the left ventricle is sufficiently large under these circumstances and if coarctation is present it is possible that the blood pressure would be higher in the upper extremities as compared to the lower extremities. In contrast, with lesser degrees of development of the left ventricle and aorta, there may be a state of balance in the aorta between the output directly from the left ventricle and that indirectly from the right ventricle through the ductus, resulting in equal blood pressures in the upper and lower limbs. A grade in severity of hypoplasia of the left ventricle, aortic valve and aortic arch may be present, however in which the aorta is perfused entirely or predominantly by the ductus and if coarctation of the aor

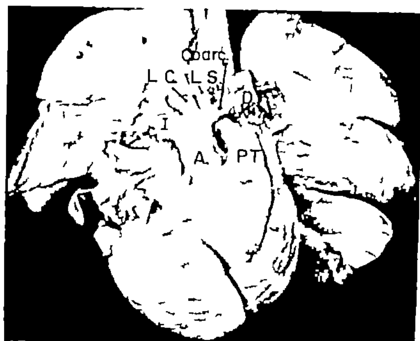


Fig 5 Specimen of the heart and great vessels from 4-day-old female infant with severe congenital unicuspid aortic stenosis. The pulmonary trunk is wider than the aorta and the patent ductus which is distal to a zone of coarctation, has been ligated

present reversed coarctation will result (Fig 3 *A* and *B*)

Mitral atresia and patent but hypoplastic aortic valve and ventricular septal defect An illustrative case is that of a male infant three days old in whom the mitral valve was atretic (Fig 4) There was a rudimentary left ventricle and a ventricular septal defect. The main pulmonary artery was twice the width of the ascending aorta. The arch of the aorta was hypoplastic in the segment between the innominate artery and the ductus. A zone of typical coarctation of the aorta was present proximal to the patent ductus, and *the left subclavian artery arose distal* to the coarctation. Blood pressure readings were not available in this case but it is likely that the pressure in the right arm *had been lower than the pressure in the* left arm and legs.

Aortic stenosis with hypoplastic left ventricle A specimen (Fig 5) illustrating severe stenosis of a unicuspid aortic valve was obtained from a female infant four

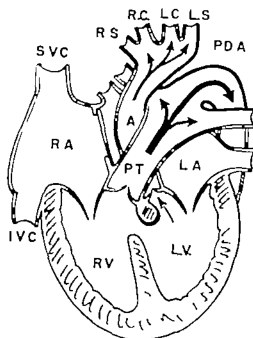


Fig 6 Diagrammatic representation of the circulation I Interruption of the aortic arch, and sub-*aortic stenosis lying distal to ventricular septal* defect.

days old in whom the blood pressure measured consecutively by the flush technique had been 40 mm Hg in the right arm and 60 mm Hg in the right leg. In the pathologic specimen the ascending aorta was smaller than the pulmonary trunk but not hypoplastic. There was a zone of tubular hypoplasia of the aortic arch between the origin of the left subclavian artery and the ductus arteriosus. A zone of typical coarctation of the aorta was situated proximal to the patent ductus. The left ventricle was hypoplastic and lined by a thick endocardial layer. The valve of the foramen ovale had herniated into the right atrium as a manifestation of a left-to-right transatrial shunt in the presence of obstruction to forward flow in the left side of the heart.

Interruption or atresia of the aortic arch with subaortic stenosis and ventricular septal defect

When the aortic arch is interrupted or atretic and the great vessels normally related the descending aorta is supplied by the right ventricle through the pul

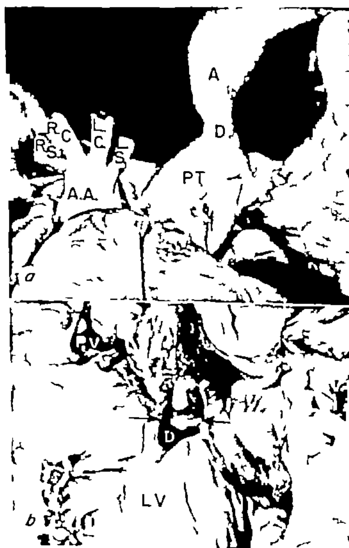


Fig. 7. Specimen of heart and great vessels in case of interruption of aortic arch with subaortic stenosis distal to ventricular septal defect in male infant of six months. A, Arrangement of the great vessels. B, Outflow tract of the left ventricle (probe) is narrowed by ridge of muscle (between arrows). The ventricular septal defect lies proximal to the subaortic stenosis.

monary artery and ductus arteriosus, while the ascending aorta is supplied by the left ventricle. A large ventricular septal defect is frequently present under these circumstances and results in equalization of pressures in both ventricles and the pulmonary artery. If obstruction beyond the ventricular septal defect is present either in the aortic valve or subaortic region of the left ventricle a lower perfusion pressure to the head and upper limbs as compared to the lower part of the body will result (Fig 6).

Variations as to the site of origin of the subclavian vessels are commonly associated with interruption of the arch[7] however and the reversed coarctation syndrome is most likely to be observed when both subclavian arteries arise from the proximal aortic segment. Should these vessels arise from the descending aorta the same levels of blood pressure would be anticipated in the femoral and subclavian arteries.

An illustrative case (Fig 7 *A* and *B*) is that of a male infant six weeks of age in whom at necropsy there was interruption of the aortic arch. The brachiocephalic vessels arose from the ascending aorta. The outflow tract of the left ventricle beyond a large ventricular septal defect was narrowed, and there also was moderate hypoplasia of the aortic valve. The descending aorta was supplied by the pulmonary artery through the ductus.

Aorta supplied entirely by the left ventricle

Stenosis of branches of arch in association with supravalvular aortic stenosis

Supravalvular aortic stenosis is an obstructive congenital deformity of the ascending aorta just distal to the level of the origins of the coronary arteries (Fig 8*A*). The obstruction may take one of three forms. In the membranous type the lesion takes the form of a simple fibrous membrane containing a single perforation. In the hypoplastic type the entire ascending aorta is hypoplastic, while in the hourglass type there is extreme thickening of the medial layer of the ascending aorta associated with an hour-glass deformity of the external aspect of this segment of the aorta.[8]

Hypoplasia of the branches of the aortic arch may be associated with supravalvular aortic stenosis, particularly when the stenosis is of the hypoplastic type.[4] In addition fibrous intimal thickening of the aortic wall surrounding the ostia of the

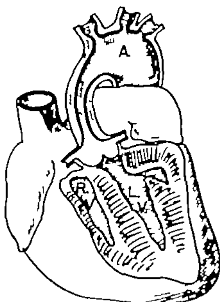


Fig 8*A* Diagrammatic representation of the circulation in the hypoplastic type of supravalvular aortic stenosis associated with stenosis of the ostia of the brachiocephalic arteries.

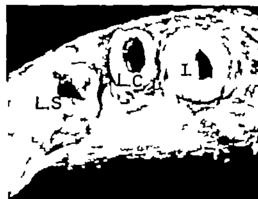


Fig 8*B* Specimen of aortic arch viewed from above from an 11-year-old boy with the hour-glass type of supravalvular aortic stenosis. Thickening of the walls of the innominate (*I*) and left common carotid (*L.C.*) arteries causes luminal narrowing of a degree that had been apparent in the aortograms. The left subclavian artery (*L.S.*) is uninvolved in this case.

brachiocephalic vessels may occur Under these circumstances, an obstruction exists to the flow of blood to the head and upper extremities and the pressure in the femoral arteries has been observed to be higher than in the brachial arteries.[9]

A specimen illustrating obstruction to the branches of the aortic arch by severe intimal thickening is illustrated in (Fig 8B) In this boy of 11 years of age the supravalvular stenosis was of the hour glass variety

Comment

The primary purpose of this review was to identify those anomalous anatomic patterns that might explain higher levels of blood pressure in the lower extremities than in the upper In two cases of this report the reversed coarctation syndrome was incomplete because the left subclavian artery arose from the higher pressured aortic compartment distal to the coarctation This would result in the pressures in the legs and left arm being higher than that of the right arm It is worthy of mention however that in certain instances without aortic coarctation similar findings may occur This state may result from the condition in which one subclavian artery fails to maintain a connection with the aorta but instead arises through the interposition of a ductus arteriosus or a ligamentum arteriosum from a pulmonary artery (so-called isolation of a subclavian artery[10,11]) The same finding may be observed in supravalvular aortic stenosis when the innominate artery is hypoplastic or its ostium narrowed by intimal thickening

In two cases of this report readings of blood pressure levels were available. The value in one instance was 20 mm Hg lower in an arm than in a leg and in the other case the pressures were equal While these values may be true reflections of the actual pressures, it is appreciated however that readings in small infants obtained by the flush method are subject to technical errors.[12] Ideally readings should be taken simultaneously by the flush technique to obtain a valid comparison between the blood pressures in the upper and lower limbs.[13]

Admittedly it is difficult to obtain accurate blood pressure readings in small infants. If however values characteristic of reversed coarctation are identified these may have important diagnostic implications as to identification of one of the conditions discussed. When reversed coarctation occurs in adults, it is apt to be the result of an acquired process, since with the exception of supravalvular aortic stenosis and obstruction of the branches of the arch the congenital types are associated with severe forms of congenital cardiac disease which do not ordinarily permit survival beyond a few months of life

Summary

The anatomic derangements which may be responsible for reversed coarctation have been reviewed This finding is most likely with congenital malformations where the aortic blood flow is derived wholly or partially from the right ventricle through a patent ductus arteriosus, and a coarctation of the aorta obstructs retrograde aortic flow as in aortic and mitral atresia or when interruption of the aortic arch is accompanied by subaortic stenosis. It may also be encountered in cases of supravalvular aortic stenosis with accompanying stenosis of the ostia of the brachiocephalic vessels. The clinical detection of reversed coarctation may be a valuable pointer to the presence of one of the more serious forms of cardiac disease particularly in the first few months of life

REFERENCES

1 Giffin, H M. Reversed coarctation and vasomotor gradient. Report of cardiovascular anomaly with symptoms of brain tumor Proc Mayo Clin. 14:561 1939
2. Shimizu, K and Sano, K Pulseless disease J Neuropath & Clin. Neurol. 1:37 1951
3 Ross, R. S and McKusick, V A Aortic arch syndromes, diminished or absent pulses in arteries arising from arch of aorta, Arch. Int Med. 92 701 1953
4 Raghib, G., Bloemendaal, R D Kanjuh, V I and Edwards, J E Aortic atresia and premature closure of the foramen ovale. Myocardial sinusoids and coronary arteriovenous fistula serving as outflow channel, Am. Heart J 70:476, 1965
5 Kanjuh V I Eliot, R. S and Edwards, J E. Coexistent mitral and aortic valvular atresia. A pathologic study of 14 cases Am J Cardiol. 15:611 1965.
6. Eliot, R. S Shone J D Kanjuh V I Rutenberg, H. D Carey L. S., and Edwards,

J. E. Mitral atresia. A study of 32 cases, Am. Heart J. 70:6, 1965.
7. Moller, J. H. and Edwards, J. E. Interruption of aortic arch. Anatomic patterns and associated cardiac malformations, Am. J. Roentgenol. 95:557, 1965.
8. Peterson, T. A., Todd, D. B. and Edwards, J. E. Supravalvular aortic stenosis, J. Thoracic & Cardiovas. Surg. 50:734, 1965.
9. Wooley, C. F., Hosier, D. M., Booth, R. W., Molnar, W., Sirak, H. D. and Ryan, J. M. Supravalvular aortic stenosis. Clinical experiences with four patients including familial occurrence, Am. J. Med. 31:717, 1961.
10. Bourassa, M. G. and Campeau, L. Combined supravalvular aortic and pulmonic stenosis, Circulation 28:572, 1963.
11. Stewart, J. R., Kincaid, O. W. and Edwards, J. E. An atlas of vascular rings and related malformations of the aortic arch system. Springfield, Ill., 1964, Charles C Thomas, Publisher, p. 76.
12. Nadas, Alexander S. Pediatric cardiology, Philadelphia, 1963, W. B. Saunders Company, p. 15.
13. Adams, P. J., Keele, Marjorie, and Baronofsky, I. Coarctation of the aorta in infants, J. Lancet 75:66, 1955.

Bronchopulmonary precapillary blood flow during cardiopulmonary bypass

*Cedric W. Deal, M.D., F.R.C.S., F.R.C.S.E.**
*Eugene Louis***
*William J. Kerth, M.D.****
*John J. Osborn, M.D.*****
*Frank Gerbode, M.D.******
San Francisco, Calif.

The bronchial circulation communicates with the pulmonary circulation by many anastomosis[1-4] (Fig. 1). The exact anatomy of these communications is still subject to discussion but in most cases the final drainage pathway is to the left atrium via the pulmonary veins.

Precapillary shunts between the bronchial arterial system and the pulmonary artery (Fig. 2) have been described and demonstrated by injection techniques[5-8] indicating a possible maximum vessel diameter of 0.5 mm.

The flow through these shunts is antegrade. During the special conditions of heart-lung bypass coupled with coronary flow, it represents the nutritional supply to the lung parenchyma. Though the return to the left atrium (which is the accumulation of many channels) has been measured, the actual flow that passes through the lung parenchyma through the bronchopulmonary arterial shunts and circulates around the alveoli has not yet been measured. In human subjects the ideal situation for assessing this flow exists under bypass conditions. When the pulmonary valve is competent and there is no contribution from the right ventricle the sole blood supply to the alveolar circulation is that blood which has traversed the bronchopulmonary precapillary arterial anastomoses.

We have been able to measure this flow under bypass conditions. Although its relation to that normally present is uncertain, the pressure relationships are not far removed from those existing preoperatively.

To measure this flow we have used an

From the Department of Cardiovascular Surgery, Presbyterian Medical Center and the Institute of Medical Sciences, San Francisco, Calif. 94115.
Supported by grants from United States Public Health Service, HE [illegible] and HE [illegible].
Received for publication April 1, [illegible].
*Fellow, Department of Cardiovascular Surgery, Presbyterian Medical Center and Department of Surgery, Stanford University School of Medicine, Palo Alto, Calif., and Recipient of Bay Area Heart Research Award.
**Summer Research Student, Institute of Medical Sciences, San Francisco, Calif., 94115.
***Director of Surgical Laboratory and Associate of Department of Cardiovascular Surgery, Presbyterian Medical Center and the Institute of Medical Sciences, San Francisco, Calif. 94115.
****Chief of Surgical Physiology, Presbyterian Medical Center and the Institute of Medical Sciences, San Francisco, Calif. 94115.
*****Chief of Cardiovascular Surgery, Presbyterian Medical Center and the Institute of Medical Sciences, San Francisco, and Clinical Professor of Surgery, Stanford University School of Medicine, Palo Alto, Calif. Address: Presbyterian Medical Center, San Francisco, Calif. 94115.

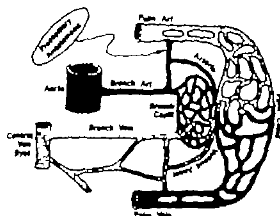


Fig. 1. Anastomoses between the bronchial and pulmonary circulation systems showing precapillary anastomoses.

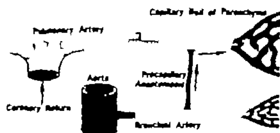


Fig. 2. Closeup view of precapillary anastomoses from Fig. 1 showing the blood flow measured by this technique.

application of the Fick principle based on CO_2.

The patients were ventilated throughout bypass with intermittent positive pressure respirators.

The data were recorded on tape and computed on a TR 20 analogue computer, the system of instrumentation being the same as that described by Segger and associates.[11] Recordings were taken during total cardiopulmonary bypass when the pulmonary flow from the right ventricle was removed by suction during right ventriculotomy or right atriotomy or when the aorta was clamped for sufficient time to eliminate the coronary return and the pulmonary valve was seen to be competent.[12] In the Fallot's tetralogy cases the aorta was clamped together with a right ventriculotomy during recording.

The p CO_2 of the arterial blood emerging from the oxygenator was kept constant and the exact p CO_2 during the recording was measured by sampling using the Astrup technique.

The percentage of CO_2 of expired air was continuously measured and the end expiratory alveolar p CO_2 was taken to be in equilibrium with the p CO_2 of the blood leaving the alveoli. The volume of CO_2 excreted was calculated by multiplying respiratory flow times the percentage of CO_2.

By means of the CO_2 dissociation curve described by Root for oxygenated blood the CO_2 volume percent of the blood entering and leaving the lung was derived from the p CO_2 values. Subtracting these values and dividing the difference into the volume of CO_2 excreted yielded the blood flow traversing the lung parenchyma. Allowances for water vapor at the temperature of operation[1] and 120 c.c. adult dead space and 60 c.c. infant dead space were made in the calculations.

A small CO_2 contribution is made from the lung metabolism causing an error which is not corrected but which is minimal at high flow rates.

Typical calculations are shown in Table I.

Results

We have divided our patients into three groups: (1) noncyanotic congenital heart disease, (2) cyanotic congenital heart disease, and (3) acquired heart disease.

Group 1. There were two atrial septal defects, two endocardial cushion defects, seven ventricular septal defects (two with mild pulmonary stenosis) and one sinus of Valsalva fistula to the right atrium (Table II). The percent of the circulation passing through the bronchopulmonary precapillary anastomoses was much higher in the atrial defects than in the ventricular defects, although one ventricular defect with mild pulmonary stenosis had a high flow.

Group 2. There were three patients with tetralogy of Fallot (Table III). In each the flow through the anastomoses was very high, amounting to 11 per cent of the circulation in one case.

Group 3. There were four patients with predominant mitral valve disease and four with aortic valve disease (Table IV). The calculated flows varied considerably

Table I. Typical calculations using Fick principle

Case	Diagnosis	Arterial pCO (mm. Hg)	Venous pCO (mm. Hg)	Arterial vol. ms (per cent)	Venous volumes (per cent)	Arteriovenous volume (per cent)	CO output	Bronchopulmonary blood flow (ml./min.)
1	Tetralogy of Fallot	35	15	47	32.5	13.5	42	311
2	ASD primum	30.4	11	43.5	28	15.5	20	129
3	AI	33	7.5	51	23	28	40	143
4	MS	22.6	8	39	26	13	20	154

ASD, atrial septal defect. AI, aortic insufficiency. MS, mitral stenosis.

Table II. Flows recorded in noncyanotic heart disease

Case	Time of record	Diagnosis	Pump flow (L./min.)	Systemic pressure (mm. Hg)	Bronchopulmonary anastomotic flow (ml./min.)	Per cent of perfusing circulation traversing anastomoses
1	10.12	ASD*	2.3	70	100	4.1
2	3.56	ASD	2.4	70	35	1.5
3	10.06	ASD primum	2.0	70	129	6.5
4	10.31	ASD primum	2.1	60	28	1.3
5	9.45	VSD and PS	2.5	70	102	4
	9.53		2.4	70	95	4
6	4.00	VSD	3.0	70	20	0.7
7	3.18	VSD	2.4	60	130	5.4
	3.30		2.4	60	67	2.8
8	9.45	VSD and PS	2.3	60	42	1.8
9	10.54	VSD	3.3	70	65	2.0
	11.04		3.0	70	57	1.9
10	9.36	VSD	3.0	100	73	2.4
	10.01		3.0	100	37	1.2
11	10.08	VSD	1.5	75	11	0.7
12	9.59	Sinus of Valsalva	3.3	70	70	2.2
	10.31	Fistula to right atrium	3.3	70	21	0.6

ASD, atrial septal defect. VSD, ventricular septal defect. PS, pulmonary stenosis.

Table III. Flows recorded in cyanotic congenital heart disease

Case	Time of record	Diagnosis	Pump flow (L./min.)	Systemic pressure (mm. Hg)	Bronchopulmonary anastomotic flow (ml./m)	Per cent of perfusing circulation traversing anastomoses
1	10.22	Tetralogy of Fallot	3.0	60	311	10.4
2	11.03	Tetralogy of Fallot	2.3	70	253	11.0
3	11.20	Tetralogy of Fallot	2.5	70	138	5.6
	11.35		2.5	70	103	4.1

Table IV Flows recorded in acquired heart disease

Case	Time of record	Diagnosis	Pump flow (L./min.)	Systemic pressure (mm. Hg)	Bronchopulmonary anastomotic flow (ml./min.)	Per cent of perfusing circulation traversing anastomoses
1	10.20	MS	3 0	70	117	3 9
2	9 40	MS	2 5	70	154	6 0
	11 11		2 0	75	117	5 8
3	1.51	MS and MI	3 6	70	274	7 6
4	11.32	MI	3 5	100	51	1 4
	12.50	TI	3 8	100	38	1 1
5	10.34	AS	3 3	80	115	3 8
	10 50	MS	2 4	80	89	3 0
6	9.52	AS	3 0	70	178	6 0
7	4 15	AI	3 6	70	143	4 0
8	10.34	AS	3 0	80	86	2 9

MS, mitral stenosis MI mitral insufficiency; TI tricuspid insufficiency AS aortic stenosis; AI, aortic insufficiency

Table V Comparison of pulmonary artery pressures in atrial septal defect and ventricular septal defect

Case	Diagnosis	P A pressure (mm Hg)	Per cent of perfusing circulation traversing bronchopulmonary anastomoses	Left-to-right shunt
1	ASD	23/12	4 1	2 1
2	ASD	22/13	1 5	2 1 1
3	ASD primum	25/12	6 5	2 5 1
4	VSD	37/16	4 0	2 7 1
5	VSD	26/12	0 7	1 7.1
6	VSD	21/4	2 0	3 6 1
7	VSD	53/10	2 4	3 8 1

ASD atrial septal defect, VSD ventricular septal defect.

one flow reaching 7 6 per cent of the circulation

In nine patients, two studies were done at separate intervals during the operation in six, the correlation was excellent In two there was a fair correlation (cases 10 and 12 Table II) and in one (case 7 Table II) the flows were 130 and 67 c.c. per minute at an interval of 12 minutes.

There seems to be a slight but consistent fall off with the length of the period between measurements.

It can be seen in all tables that the blood pressure during perfusion varied between 60 and 100 mm Hg the majority falling between 70 and 80 mm Hg

The pulmonary artery pressure has been compared in the atrial septal and ventricular septal defects (Table V) The anastomotic flow does not seem to be related to this pressure.

The pulmonary and systemic pressures are presented with their gradients in 17 cases together with the calculated anastomotic flow (Table VI) The gradients vary between 15 and 142 mm Hg Those with small gradients, i e. cases 3 and 9 (gradients 15 and 26 mm Hg) have small anastomotic flows (28 and 11 c.c. per minute, respectively) Those with high gradients, i.e., cases 6 and 16 (gradients 107 and 142 mm. Hg) have high flows

Table VI Haemodynamic data from catheter studies related to calculated bronchopulmonary anastomotic flow

Case	Diagnosis	P.A. pressure (mm. Hg)	Systemic pressure (mm. Hg)	P gradient (mm. Hg)	Pulm. flow (L./min.)	Anastomotic flow (c.c./min.)
1	Sinus of Valsalva fistula	26/13	160/64	134	16.8	70
2	Endocardial cushion defect	25/12	97/50	72	5.9	129
3	Endocardial cushion defect	67/12	83/60	15	—	48
4	ASD	22/13	100/75	78	4.6	35
5	ASD	23/12	100/80	77	—	100
6	VSD	27/12	134/82	107	5.9	130
7	VSD	21/4	88/45	67	—	42
8	VSD	37/6	112/59	75	6.46	102
9	VSD	53/10	79/50	26	4.5	11
10	Tetralogy of Fallot	18/8	119/58	101	—	311
11	MS	68/34	117/70	49	3.5	117
12	MS	80/32	146/66	66	3.1	154
13	MS, MI	39/19	120/63	81	5.2	274
14	MI, TI	57/29	134/57	77	—	51
15	AS, MS	33/15	122/64	89	3.2	115
16	AI	29/13	171/64	142	5	143
17	AS	22/12	134/78	112	5.5	86

ASD, atrial septal defect; VSD, ventricular septal defect; MS, mitral stenosis; MI, mitral insufficiency; TI, tricuspid insufficiency; AS, aortic stenosis; AI, aortic insufficiency.

(130 and 143 c.c. per minute) but there is no consistent pattern between these extremes.

Discussion

Pump[3] reviewed the literature on the anatomy of precapillary bronchopulmonary anastomoses in the normal lung and described many large anastomotic vessels, some of which had a coiled nature. Microscopic study of these anastomoses by Hayek[4] revealed sphincters around the larger anastomoses possibly controlling the flow. Turner-Warwick failed to demonstrate these vessels in normal lungs but found consistent large precapillary anastomoses in cyanotic conditions.

Using a closed-loop pulmonary circulation in dogs Awad and co-workers[11] showed that the bronchial arteries contributed considerably to the pulmonary circulation, but he could not distinguish the flow through the precapillary anastomoses.

Using similar conditions to ours (bypass with interrupted coronary return) Cartwright and associates[12] recorded collections from the left atrium in dogs. Their results were 8.8 ± 4.9 ml. per minute which was 0.7 per cent of the systemic flow. This collection represented the total bronchial flow reaching the left atrium by the many devious connections of the bronchial artery. The figures of Cartwright and associates[12] are in agreement with the reported data of others,[1] though these are still in dogs.

We have measured only that part of the bronchial blood flow which has actually reached the lung parenchyma and alveolar circulation through the bronchopulmonary precapillary anastomoses. Our calculated parenchymal blood flows were high in comparison to the total collections described by others.[12, 17] Many factors may contribute. Our figures are from man as opposed to dogs. Many of the lungs dealt with in our study are abnormal, having been subject to prolonged altered hemodynamics. These altered hemodynamics would probably promote and enlarge any existing collateral channels. Under the conditions of pump oxygenator bypass the pulmonary artery pressure is low, increasing the normal systemic pulmonary gradient, and this might represent the maximum flow possible. The steady systemic pressures may also serve to increase the flow

and if the anastomoses are under sphincteric control as described by Hayek, it is probable that they may be dilated during bypass. Certainly the possibility of a large flow is consistent with the large diameter (0.5 mm.) of the vessels described by Pump.[3]

It was observed that the flows recorded in the atrial defects were larger than those in the ventricular defects. The pulmonary artery pressures in the two defects were compared (Table V) to determine whether there was a decreased gradient in the ventricular defects inhibiting collateral formation, but the differences were not significant. When the pulmonary systemic gradient in Table VI is considered it can be seen that there is a marked difference between those with high gradients and those with low gradients even though there is no consistent pattern in between. It seems logical that this gradient would play an important part in the development of these anastomoses.

Injection studies by Turner Warwick demonstrated large anastomotic vessels in cyanotic heart disease. As expected, our flows were very large in the cyanotic group suggesting that in these cases the bronchial blood supply contributes in a major degree to the oxygenation system of the body. In one instance it amounted to 11 per cent of the circulation.

In the acquired group the flows were about 5 per cent of the perfusing circulation. The variation in these figures may reflect the length of time the lungs have been subject to the abnormal heart conditions and may also be influenced by the older ages in this group.

Summary

A method of calculating the blood flow traversing bronchopulmonary anastomoses during cardiopulmonary bypass is presented, based on the CO_2 Fick principle.

A total of 23 patients have been studied. Bronchial alveolar flow varied with the type of cardiac lesion and was often considerable, amounting to 11 per cent of the circulation in one patient with tetralogy of Fallot.

We wish to thank the Anaesthetic Department for the forbearance that made this article possible, and Mr. Stanley Elliott for his valuable technical assistance.

REFERENCES

1. Lapp, H.: Über die Sperarterien der Lunge und die Anastomosen Zwischen A. bronchialis und A. pulmonalis, Über ihre Bedeutung, Insbesondere fur die Entstehung des Hamorrhagischen Infarktes, Frankfurt Ztschr. Path. 62:537, 1931.
2. Tobin, C. E.: The bronchial arteries and their connections with other vessels in the human lung, Surg. Gynec. & Obst. 95:741, 1952.
3. Pump, K. K.: The bronchial arteries and their anastomoses in the human lung, Dis. Chest 43:245, 1963.
4. Hayek, H. V.: Die menschliche Lunge, Berlin, 1953, Springer Verlag.
5. Verloop, M. C.: The arteriae bronchiales and their anastomoses with the arteria pulmonalis in the human lung: micro-anatomical study, Acta anat. (Basle) 5:171, 1948.
6. Kovacs, G. S.: Clinical significance of bronchopulmonary collateral circulation, Thesis, Budapest, 1965.
7. Liebow, A. A., Hales, M. R., and Bloomer, W. E.: Relation of bronchial to pulmonary vascular tree, *In* pulmonary circulation: an international symposium, New York, 1959, Grune & Stratton, Inc.
8. Heimburg, P.: Bronchial collateral circulation in experimental stenosis of the pulmonary artery, Thorax 19:306, 1964.
9. Turner Warwick, M.: Precapillary systemic pulmonary anastomoses, Thorax 18:225, 1963.
10. Beer, R., and Loeschcke, G. C.: Veränderungen der Lungenfunktion nach Operationen mit der Herz Lungen Maschine, Der Anaesthesist 12:306, 1963.
11. Segger, F., Osborn, J. J., Elliott, S., and Gerbode, F.: Oxygen uptake and pulmonary function by analogue computation from rapid sensors, J. M. Res. Eng. In press.
12. Cartwright, R. S., Lim, T. P. K., Luft, U. C., and Palich, W. E.: Pathophysiological changes in the lungs during extracorporeal circulation, Circulation Res. 10:131, 1962.
13. Root, R. W.: 67 blood CO absorption as function of CO pressure. Man. *In* Dittmer, D. S., and Grebe, R. M., editors: Handbook of Respiration, Philadelphia, 1958, W. B. Saunders Company, p. 64.
14. Comroe, J. J. J.: The lung, Chicago, 1962, Year Book Medical Publishers, Inc. 2:334, Table 36.
15. Aad, J. A., Ghys, R., Lou, W., Beaulieu, M., and Lemieux, M.: Hemodynamic aspects of the pulmonary collateral circulation, J. Thoracic and Cardiovas. Surg. 50:596, October, 1965.
16. Bruner, H. D., and Schmidt, C. F.: Blood flow in the bronchial artery of the anesthetized dog, Am. J. Physiol. 118:648, 1947.
17. State, D., Salisbury, P. F., and Weil, P.: Physiologic and pharmacologic studies of collateral pulmonary flow, J. Thoracic Surg. 34:599, 1957.

Experimental and laboratory reports

Analysis of a cardiac cycle of the left side of the heart in cases of left ventricular overloading or damage with the ultrasonic Doppler method

Yasukaru Yimura M D M Sc
Hirokide Matsuo M D
Shigeki Mochizuki M D
Kazuko Aoki M D
Onkyo Wada M D
Hiroshi Abe M D
Osaka Japan

It is considered that the motion of the heart is influenced by conditions of the heart and abnormalities of the heart result in disturbances of the motion. Therefore, registration of the motion of the heart may allow one to get information on cardiac function. So far there have been reports on periodical mechanical phenomena of the heart in reference to intracardiac pressure, apexcardiogram, kinetocardiogram, carotid arterial pulse, phonocardiogram, and so on, but these methods are indirect or fairly troublesome. Ultrasonic methods enable one to obtain direct information on the inner aspect of the heart without any burden to the patient. The ultrasonic pulse method[1] and the Doppler method[1-8] have been used in detecting the motion of the heart, especially of the valves. The motion curve of the anterior mitral cusp is obtained with the former method. Detection of the semilunar valve is not possible with the former method, but with the latter method one can obtain information on the motion of the semilunar valve as well as the mitral valve.

In the present study the times of occurrence of the mitral valve and the aortic valve motions were detected with the Doppler method. Also detection of the time of occurrence of the valve motion led one to study changes of duration in each phase in a cardiac cycle under various conditions of the heart.

An approach was made from this aspect to essential hypertension with or without cardiac involvement, arteriosclerotic heart disease, and aortic regurgitation.

Methods

The ultrasonic Doppler method has been devised to obtain information on the motion of a moving object on the basis of Doppler shift on the frequency of the continuous ultrasonic wave reflected from the object. When a reflected wave is received by a receiving part of the transducer and superposed with a transmitter wave

From the First Department of Medicine, Osaka University Medical School, Osaka, Japan.
Received for publication Oct. 11, 196[illegible].

which is directly led from a sending part to the receiving part of the transducer there occurs a beat between the two waves. As reported previously [11] the frequency of the beat is proportional to the speed of a reflecting spot of the ultrasonic beam on the object in a direction parallel to the ultrasonic beam. This beat allows one to obtain information on the time of occurrence and the speed of the movement of the object. [4,11]

The Doppler signal which represents movements of the valve can be detected with proper application of a transducer placed on the precordium. The valves, which rapidly move in the heart, are related with a beat higher in its frequency than any other beat related with other parts of the heart. The details about identification of each valve have been reported previously. [11,13]

In the present study ultrasound of 3 megacycles per second was used. The Doppler signal of the mitral valve is shown in Fig. 1. The top of the figure shows a frequency-spectrogram of the signal. In the spectrogram the abscissa represents time, the ordinate, frequency, and the density, the intensity of the component of the frequency concerned. This spectrogram enables one to observe changes of frequency of the Doppler signal in reference to time. The signal Mc is a signal related to a closing of the mitral valve and Mo is that related to an opening. Mps and Md are also related to the valve motion as shown in other papers. [1] According to the principles of the Doppler method, changes of frequency of the Doppler signal in reference to time indicate changes of speed of the reflecting spot, with allowance of a slight change of the spot on the object during a cardiac cycle in accordance with the valvular movements. The Doppler signal which was recorded with filters is shown at the base of Fig. 1. The filter was a combination of a band pass filter, the center of the frequency response of which was 1 000 cycles per second (c.p.s.) and Q of which was 4, and a high pass filter, the nominal frequency and the characteristics of which were 680 c.p.s. and 18 db./oct., respectively. With these filters high frequency components in the Doppler signal which are related to rapid movements of the valve can be picked out. As shown in the relationship between the Doppler signal and the spectrogram in Fig. 1, the Doppler signal recorded with the filter can detect a rapid stage of the motion of the valve. The onset and completion of the Doppler signal recorded with the filter are the times when the frequency of the signal becomes higher and lower than 1 000 c.p.s., respectively, i.e., the times when the speed of the valve becomes higher and lower than 250 mm. per second, respectively. Thus, the Doppler signal recorded with the filter is advantageous in defining the onset or completion of rapid movement at the time of opening and closing of the valve, respectively.

In the present study, the completion of signal related to the closing of the valve was defined as the time of closing of the

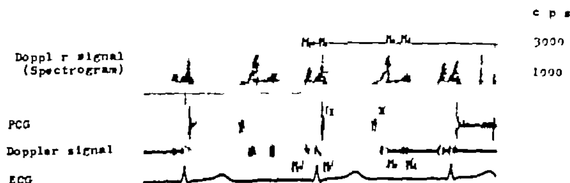


Fig. 1. Doppler signal of the mitral valve recorded at the third intercostal space near the left sternal edge of healthy subject. Top, spectrogram of the Doppler signal. The abscissa indicates time, the ordinate, frequency, the darkness, the intensity of the concerned frequency component. Bottom, Doppler signal recorded on oscillogram through filters.

valve, and the onset of signal related to the opening of the valve was defined as the time of opening. Thus, each phase of a cardiac cycle was defined as follows.

1. The electromechanical latent time of the left ventricle. The interval from the beginning of the QRS complex in the ECG to the completion of the closing of the mitral valve expressed by a Q-Mc interval.*

2. The isometric contraction time. The interval from the completion of the closing of the mitral valve to the onset of the opening of the aortic valve expressed by an Mc-Ao interval.

3. The tension period. The interval from the beginning of the QRS complex to the onset of the opening of the aortic valve expressed by a Q-Ao interval.

4. The isometric relaxation time. The interval from the completion of the closing of the aortic valve to the onset of the opening of the mitral valve expressed by an Ac-Mo interval, i.e. the interval from the onset of the main component of the second heart sound to the opening of the mitral valve, the II-Mo interval, because the onset of the main component of the second heart sound usually coincides with the completion of the closing of the aortic valve.[13]

In the present study the Doppler signal of the valve was recorded on oscillopaper with the ECG and the phonocardiogram which was picked up in the apical area.

Materials

The persons examined were grouped as follows.

1. Essential hypertension (systolic pressure over 150 mm. Hg and/or diastolic pressure over 90 mm. Hg), 171, divided into the following groups.
   A. Hypertension without electrocardiographic signs of myocardial involvement, 77.
   B. Hypertensive heart disease, 94.
      a. Patients with nonspecific ST-T abnormalities other than those described in the next item (b).
      b. Patients with T-wave inversion and upwards convex ST depression in those leads where the left ventricular potentials are transmitted. In the following description and figures these ST-T abnormalities are grouped as left ventricular strain pattern.
      c. Conditions which satisfied one or more of following criteria: $R_I + S_{III} \geq 25$ mm., $R_{aVL} > 11$ mm., $R_V > 26$ mm. and $R + S > 35$ mm. In the following description these are grouped as left ventricular hypertrophy.
      d. Patients with electrocardiographic signs of both left ventricular strain pattern and left ventricular hypertrophy as described in item b and c.
2. Arteriosclerotic heart disease, 48.
3. Congestive heart failure due to hypertensive heart disease or arteriosclerotic heart disease, of Class III or higher in the New York Heart Association classification of functional capacity, 12.
4. Aortic regurgitation, 28, divided into the following groups.
   A. Patients with electrocardiographic signs of

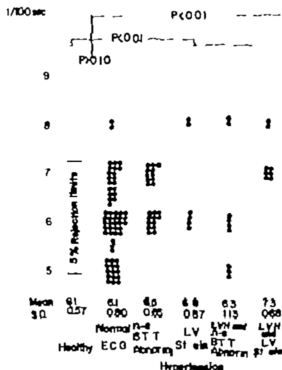


Fig. 2. The electromechanical latent time of the left ventricle (Q-M interval) in reference to changes in ECG. Normal ECG = hypertensive cases without electrocardiographic signs of myocardial involvement (Group 1A); n.-s. ST-T abnorm. = hypertensive cases with nonspecific ST-T abnormalities (Group 1 Ba); LV strain = hypertensive cases of left ventricular strain pattern (Group 1 Bb); LVH and n.-s. ST-T abnorm. = hypertensive cases of left ventricular hypertrophy and nonspecific ST-T abnormalities (Group 1 Bc); LVH and LV strain = hypertensive cases of left ventricular hypertrophy and left ventricular strain pattern (Group 1 Bd).

*In the author's previous report[1] measurement of Mc and Ac times referred to their beginnings, but in the present report they referred to their completion. Regarding Mo and Ao, they referred to their beginning in both reports.

diastolic overloading of the left ventricle in Cabrera classification that is high, delayed R and elevated T waves in those leads where the left ventricular potentials are transmitted.[19]

B Severe cases with ST depression and T inversion in addition to the high, delayed R wave as mentioned in the previous item

5 Healthy subjects used as controls 52

Results

1 Essential hypertension

THE ELECTROMECHANICAL LATENT TIME OF THE LEFT VENTRICLE. The Q-Mc interval in hypertensive patients without electrocardiographic abnormalities (Group 1A) did not differ from that in healthy subjects ($p > 0.10$). It was longer in four groups of patients with hypertensive heart disease (Groups 1 Ba, 1 Bb, 1 Bc and 1 Bd) than in healthy subjects (Group 5) ($p < 0.01$) (Figs. 2 and 3) and when statistically examined in terms of five groups of hypertensive patients as a whole was found to be significantly different ($p < 0.01$).

THE ISOMETRIC CONTRACTION TIME OF THE LEFT VENTRICLE. The Mc-Ao interval was longer in hypertensive patients without *electrocardiographic abnormalities than in* healthy subjects ($p < 0.01$) and when statistically examined *in terms of five groups of hypertensive patients as a whole* was found to be significantly different ($0.01 < p < 0.05$) (Fig. 4).

THE TENSION PERIOD OF THE LEFT VENTRICLE. The Q-Ao interval was longer in hypertensive patients without electrocardiographic abnormalities than in healthy subjects ($p < 0.01$) and there existed a relationship between degrees of cardiac involvements and those of prolongation of the tension period ($p < 0.01$) (Figs. 5 and 6).

Possible factors which seem to be responsible for a prolongation of the tension period are an elevation of diastolic pressure of the aorta and a frequent bradycardia in hypertensive patients as well as the presence of myocardial involvements, so roles of these factors in the prolongation were examined with regression planes, as shown in Addendum I. This analysis indicated that duration of the Q-Ao interval

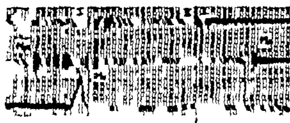




Fig. 3 Top, Doppler signal of the mitral valve in a case of hypertensive heart disease. The Q-Mc interval and the II-Mo interval are prolonged. Bottom, Doppler signal of a healthy subject presented for comparison.

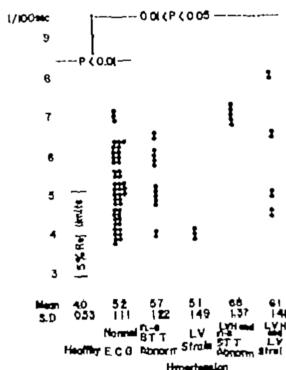


Fig. 4. The isometric contraction time of the left ventricle (an Mc Ao Interval)

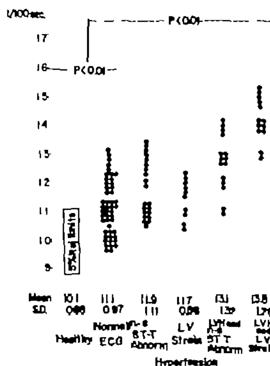


Fig. 5. The tension period of the left ventricle (Q-Ao Interval).

depended on the diastolic pressure and the heart rate as well as on the presence of myocardial involvements. But as shown in Addendum III it was revealed that the presence of myocardial involvements was more closely related to a prolongation of the tension period than the diastolic pressure and the heart rate.

THE ISOMETRIC RELAXATION TIME OF THE LEFT VENTRICLE. The II Mo interval was prolonged in cases of hypertensive patients without electrocardiographic abnormalities ($p < 0.01$) and was further prolonged in patients with hypertensive heart disease especially those with left ventricular hypertrophy and strain pattern ($p < 0.01$) (Figs. 3 and 7).

Statistical analyses were applied in pursuing factors responsible for changes in the isometric relaxation time as done in the tension period (see Addenda II and III). These analyses also showed that myocardial involvements were most responsible for the prolongation of the isometric relaxation time.

2. Arteriosclerotic heart disease

THE ELECTROMECHANICAL LATENT TIME. The electromechanical latent time of the left ventricle (a Q-Mc interval) was longer in patients with arteriosclerotic heart disease (Group 2) than in healthy subjects used as control ($p < 0.01$) (Fig. 8 *A*).

THE ISOMETRIC CONTRACTION TIME. The isometric contraction time of the left ventricle (an Mc Ao interval) was longer in patients with arteriosclerotic heart disease than in healthy subjects ($0.01 < p < 0.05$) (Fig. 8 *B*).

THE TENSION PERIOD. The tension period of the left ventricle (a Q-Ao interval) was also prolonged ($p < 0.01$) (Fig. 8 *C*).

THE ISOMETRIC RELAXATION TIME. The isometric relaxation time of the left ventricle (a II Mo interval) was prolonged ($p < 0.01$) (Fig. 8 *D*). In this case changes were more marked than in the above-mentioned three phases.

3. Congestive heart failure due to hypertensive heart disease or arteriosclerotic heart disease. When patients developed congestive heart failure, the above mentioned changes in phases of a cardiac cycle were further remodified under the influence of congestive heart failure.

The electromechanical latent time (a

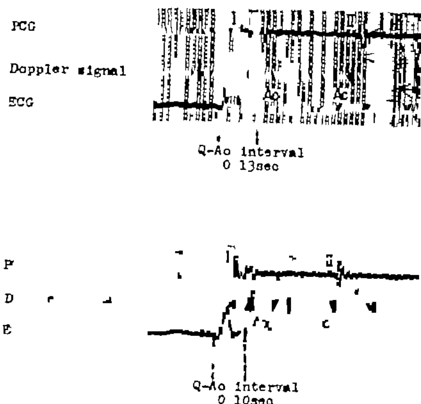


Fig 6 Top, Doppler signal of the mitral valve in case of hypertensive heart disease The Q-Ao interval is prolonged. Bottom Doppler signal of healthy subject presented for comparison



Fig 7 The isometric relaxation time of the left ventricle (a II Mo interval)

Q-Mc interval) was more prolonged in cases of congestive heart failure due to hypertensive heart disease or due to arteriosclerotic heart disease (Group 3) than in compensated cases of the same diseases. Almost all cases were plotted out of 5 per cent rejection limits of healthy subjects (Fig 9 A)

The isometric contraction time (an Mc Ao interval) was more prolonged in decompensated cases than in compensated ones ($p < 0.01$) (Fig 9 B)

The tension period (a Q-Ao interval) in cases of congestive heart failure was also markedly prolonged—to 0.18 seconds at maximum In those decompensated cases it was beyond the upper limit of rejection of 5 per cent of normal and was longer than in compensated cases ($p < 0.01$) (Fig 9 C) When congestive heart failure was subsided the remodified tension period returned to the previous stage.

The prolonged II Mo interval showed a tendency to return to a normal range when patients developed congestive heart failure. It was shorter in cases of congestive heart

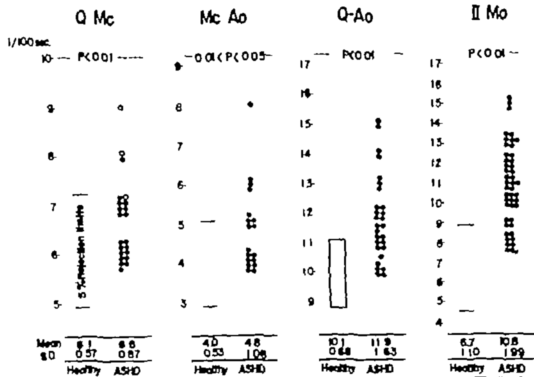


Fig. 8 Durations of phases in cardiac cycle on the left side of the heart in cases of arteriosclerotic heart disease A Electromechanical latent time B isometric contraction time C, tension period D isometric relaxation time.

Q Mc
Mc Ao
Q-Ao
II-Mo
1/100 sec
P<0.01
P<0.01
P<0.01
P<0.01
5% Rejection limits
Mean 6.0 6.6 8.2
SD 0.87 0.83 0.96
Healthy Compensated Decompensated
HHD, ASHD
4.0 5.5 6.9
0.53 1.37 1.8
Healthy Compensated Decompensated
HHD, ASHD
10.1 12.4 15.3
0.68 1.52 1.65
Healthy Compensated Decompensated
HHD, ASHD
6.7 11.6 7.8
1.10 2.13 2.02
Healthy Compensated Decompensated
HHD, ASHD

Fig. 9 Durations of phases in cardiac cycle on the left side of the heart in *decompensated cases shown comparatively* with those in compensated cases. A Electromechanical latent time B isometric contraction time C, tension period; D isometric relaxation time.

failure than in compensated cases ($p < 0.01$) (Fig 9 *D*) When congestive heart failure was subsided the isometric relaxation time (a II Mo interval) regained the previous stage.

4 *Aortic regurgitation* The electromechanical latent time (a Q-Mc interval) was slightly prolonged in cases with electrocardiographic signs of diastolic overloading of the left ventricle (Group 4A) in comparison with healthy subjects ($0.05 < p < 0.10$) It was also prolonged in severe cases with ST depression and T inversion in addition to the high delayed R wave (Group 4B) There was no difference between Groups 4A and 4B ($p > 0.10$) (Fig 10 *A*)

The isometric contraction time (an Mc Ao interval) in Group 4A was shortened in comparison with healthy subjects ($p < 0.01$) (Fig 10 *B*)

The tension period (a Q-Ao interval) was shorter in Group 4A than in healthy subjects ($0.01 < p < 0.05$) It seemed to be slightly longer in Group 4B than in Group 4A, but this difference was not statistically significant (Fig 10 *C*) Also it was markedly shortened in Group 4B in comparison with cases of hypertensive heart disease (Groups 1Ba-d)

The isometric relaxation time (a II Mo interval) in Group 4A did not differ from that in healthy subjects. It seemed to be rather prolonged in Group 4B but there was no difference between Groups 4A and 4B (Fig 10 *D*) It was shorter in Group 4B than in cases of hypertension as a whole

These results are summarized in Table I and Fig 11

Discussion

Since Wiggers'[38] report duration of phases in a cardiac cycle has been studied as one of the items which represent cardiac function. The status of the myocardium hemodynamic conditions such as intracardiac pressures, the length of a cardiac cycle mobility of the valves, neurohumoral regulations etc have been considered to be factors which influence changes in duration of phases in a cardiac cycle Therefore an analysis of the mode of changes in duration of phases in a cardiac cycle in the presence of various underlying pathological conditions may allow one to obtain infor

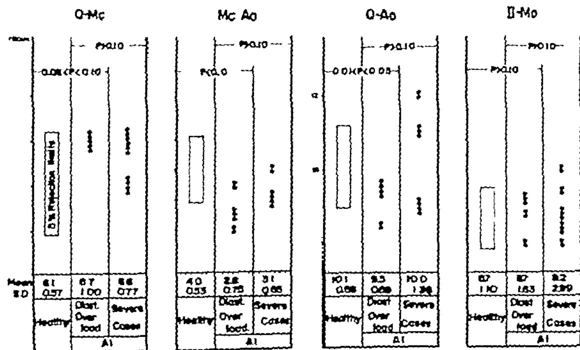


Fig 10 Durations of phases in a cardiac cycle on the left side of the heart in cases of aortic regurgitation *A* Electromechanical latent time *B* Isometric contraction time *C*, tension period *D* Isometric relaxation time. *AI* aortic regurgitation. Diast. overload, cases of electrocardiographic signs of diastolic overloading (Group 4A). Severe cases, Group 4B

mation on changes in the above mentioned pathophysiological factors. It may also give useful material for diagnosis, differential diagnosis, and evaluation of the grade of pathological conditions. From this viewpoint an analysis of the left side of the heart was performed in patients with overloading and/or damage of the left ventricle.

The electromechanical latent time. So far the electromechanical latent time has been measured phonocardiographically as the Q-I interval. Studies with ultrasound revealed that the main vibration of the first heart sound begins immediately after the completion of closing of the foregoing one of the two atrioventricular valves.[1, 14] The mitral valve usually closes a little earlier than the tricuspid valve,[14] so the Q-I interval is considered to change in almost the same manner as the Q-Mc interval. Weissler and co-workers,[27] Sakamoto and co-workers,[23] Gibney and co-workers[22] and Puchner and co-workers[1] reported a prolongation of the Q-I interval in cases of hypertension in contrast to the denial of Holldack,[23] and Yoshimura and co-workers.[24] Sakamoto and co-workers[23] presumed a participation of an elevation of left atrial pressure in a prolongation of the Q-I interval. In the present study the electromechanical latent time did not show a prolongation in cases of hypertension without electrocardiographic abnormalities, while it was prolonged with a statistical significance in those with myocardial involvements. Thus these discrepancies among investigators concerning a prolongation of the Q-I interval might have resulted from differences of conditions of materials.

Factors which are considered responsible for a prolongation of the electromechanical latent time are as follows.

The first possible factor is an impairment of contractility of the myocardium. The fact that the severer the electrocardiographic findings, the more marked the prolongation of the electromechanical latent time suggested the responsibility of the status of myocardium itself. This in-

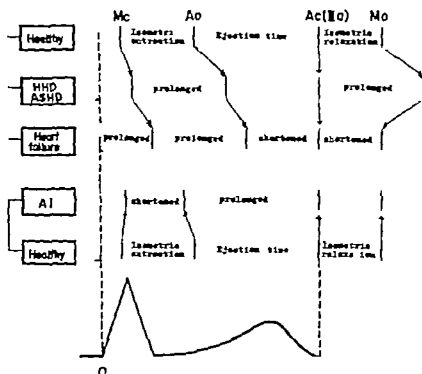


Fig. 11. Changes in phases in cardiac cycle on the left side of the heart in cases with left ventricular overloading and/or damage.

failure than in compensated cases ($p < 0.01$) (Fig 9 *D*). When congestive heart failure was subsided, the isometric relaxation time (a II-Mo interval) regained the previous stage.

4. *Aortic regurgitation.* The electromechanical latent time (a Q-Mc interval) was slightly prolonged in cases with electrocardiographic signs of diastolic overloading of the left ventricle (Group 4A) in comparison with healthy subjects ($0.05 < p < 0.10$). It was also prolonged in severe cases with ST depression and T inversion in addition to the high delayed R wave (Group 4B). There was no difference between Groups 4A and 4B ($p > 0.10$) (Fig 10 *A*).

The isometric contraction time (an Mc-Ao interval) in Group 4A was shortened in comparison with healthy subjects ($p < 0.01$) (Fig 10 *B*).

The tension period (a Q-Ao interval) was shorter in Group 4A than in healthy subjects ($0.01 < p < 0.05$). It seemed to be slightly longer in Group 4B than in Group 4A, but this difference was not statistically significant (Fig 10 *C*). Also, it was markedly shortened in Group 4B in comparison with cases of hypertensive heart disease (Groups 1Ba–d).

The isometric relaxation time (a II-Mo interval) in Group 4A did not differ from that in healthy subjects. It seemed to be rather prolonged in Group 4B, but there was no difference between Groups 4A and 4B (Fig 10 *D*). It was shorter in Group 4B than in cases of hypertension as a whole.

These results are summarized in Table I and Fig 11.

Discussion

Since Wiggers'[39] report, duration of phases in a cardiac cycle has been studied as one of the items which represent cardiac function. The status of the myocardium, hemodynamic conditions such as intracardiac pressures, the length of a cardiac cycle, mobility of the valves, neurohumoral regulations, etc., have been considered to be factors which influence changes in duration of phases in a cardiac cycle. Therefore, an analysis of the mode of changes in duration of phases in a cardiac cycle in the presence of various underlying pathological conditions may allow one to obtain infor-

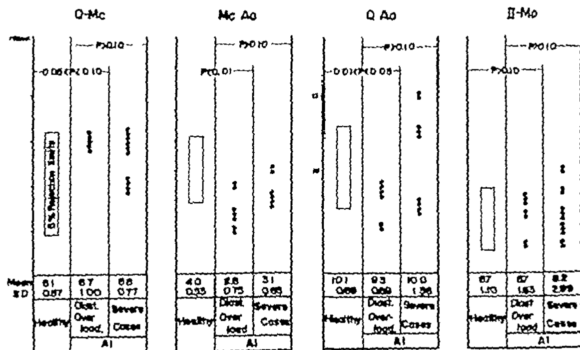


Fig. 10. Durations of phases in cardiac cycle on the left side of the heart in cases of aortic regurgitation. *A*, Electromechanical latent time. *B*, Isometric contraction time. *C*, tension period. *D*, Isometric relaxation time. *AI*, aortic regurgitation. Diast. overload, cases of electrocardiographic signs of diastolic overloading (Group 4A). Severe cases, Group 4B.

and/or damage

Isometric contraction time			*Tension period*			*Isometric relaxation time*		
Cases	*Mean*	*Standard deviation*	*Cases*	*Mean*	*Standard deviation*	*Cases*	*Mean*	*Standard deviation*
26	4 0	0 53	28	10 1	0 68	52	6 7	1 10
48	5 2	1 11	49	11 1	0 97	74	10 2	1 70
16	5 7	1 22	23	11 9	1 11	41	11 1	2 04
7	5 1	1 49	11	11 7	0 88	18	11 6	1 51
8	6 8	1 37	18	13 1	1 32	16	12 4	1 50
9	6 1	1 41	16	13 8	1 28	18	14 1	1 71
20	4 8	1 08	29	11 9	1 63	47	10 8	1 99
9	6 9	1 48	11	15 3	1 65	12	7 8	2 02
8	2 8	0 75	8	9 3	0 69	10	6 7	1 63
9	3 1	0 65	12	10 0	1 36	15	8 2	2 99

such difference in opinions between the present study and Sambhi's report is left to be studied in future.

In the present study the isometric contraction time was shortened in cases of aortic regurgitation. Gibney and colleagues[17] obtained similar results following measurements of carotid arterial pulse so did Moskovitz and Wilder[31] experimentally This shortening may be due to a large amount of ventricular blood and reduced pressure difference in this period between the aorta and the left ventricle resulting from a low diastolic pressure of the aorta.

The tension period. Holldack[28] reported that his "Anspannungszeit" an interval from the beginning of the QRS to the carotid notch subtracted by 0.05 second was 0.091 second. Braunwald and colleagues[1] measured the tension period to be 0 115 second in reference to pressure measurements with heart puncture in thoracotomy Harrison and colleagues[22] revealed that there occurred a deflection in the kinetocardiogram resulting from the onset of a ventricular ejection 0 105 second after the beginning of the QRS. The tension period measured with the Doppler method is 0 101 second on an average in healthy subjects, which gives support to the above mentioned reports.

Among the factors considered influential in the duration of the tension period are the pressure difference between ventricle and aorta in end-diastole, the contractility of myocardium the speed of contraction and the ventricular filling Lange[34] revealed a correlation between the duration of tension period and the heart rate.

It was presently revealed that there was a correlation between the diastolic arterial pressure and the duration of tension period the Q-Ao interval as well as between the heart rate and the latter But statistical analyses showed that the presence of myocardial involvements were the most significant factor of the above mentioned three factors. The duration of the Q-Ao interval did not always change in correspondence to the change of blood pressure in a short time.[17] Consequently the prolongation of the Q-Ao interval in hypertensive patients is not considered to have resulted directly from hemodynamic conditions represented by blood pressure but from the changes in the myocardium secondary to hypertension. A prolongation of the Q-Ao interval in patients with arteriosclerotic heart disease seemed to support an important role of the myocardium Also, Simonson and Nakagawa revealed with the impedance plethysmogram

that there occurred a delay in the onset of aortic volume pulse in cases with myocardial ischemia or myocardial degeneration.

The Q-Ao interval was more markedly prolonged in congestive heart failure. Holldack[25] and Hashimoto[17] obtained similar results with other procedures.

The above mentioned discussion lead one to an assumption that a prolonged Q-Ao interval in hypertensive patients without electrocardiographic abnormalities can be interpreted as a manifestation of latent myocardial involvements. Hashimoto[17] reached the same opinion from another approach. Here should be cited a report by Lange[26] that the Anspannungszeit was longer in healthy subjects over 50 years old than in those under 50 even with due regard to the heart rate.

The Q-Ao interval was shortened in patients with aortic regurgitation irrespective of the presence of electrocardiographic signs of myocardial involvement. It is considered that a markedly low diastolic pressure of the aorta causes an early opening of the aortic valve overcoming the influence of myocardial conditions, which is considered to delay the aortic opening.

The isometric relaxation time. The isometric relaxation time was prolonged in hypertensive patients, especially in those with electrocardiographic signs of myocardial involvement. Factors influential to the duration of this period may include the diastolic pressure of the aorta, conditions of myocardium in a conversion phase from contraction to relaxation, speed of relaxation, venous return, and atrioventricular pressure difference. The first two factors, i.e., the low diastolic pressure and the presence of myocardial involvement, may act to prolong the II-Mo interval. Statistical analyses referred to the presence of electrocardiographic signs of myocardial involvements, diastolic blood pressure and heart rate revealed that the presence of myocardial involvements was the most influential. There was also a certain correlation between the diastolic pressure and duration of the II-Mo interval. But the II-Mo interval did not always change following changes in diastolic pressure in a short time.[17] Therefore, it is considered that the duration of the II-Mo interval is not directly correlated to diastolic pressure. This correlation is considered to be secondary through myocardial involvements due to hypertension.

The above mentioned prolongation of the isometric relaxation time supports a consideration that there were certain disturbances in the mechanism of a conversion phase from systole to diastole or in speed of relaxation in early diastole. Millahn[16] pointed out that the speed of relaxation was slow in the athletic heart or in subjects with parasympathicotony, and so the tone of the myocardium in these cases seemed to be high. Also, there may be a slowing of the speed of relaxation secondary to the increased tone of the myocardium in hypertensive patients.

Dodge and co-workers[29] noted changes in elasticity or in distensibility of the myocardium in diastole in cases of heart disease, so also did Mitchell and co-workers[4] experimentally. These findings seem to be highly suggestive of a prolongation of the isometric relaxation time.

So far, ST-T changes in hypertrophied hearts have been interpreted as a delay of a repolarization process in the outer layer of myocardium. The finding that a prolongation of isometric relaxation time was marked in cases with ST-T changes may allow one to suggest a close relationship between them in their mechanism.

The II-Mo interval was prolonged even in cases of arteriosclerotic heart disease. Also this finding supports an important role of conditions of the myocardium in prolongation of the II-Mo interval in cases of hypertensive heart disease.

The prolongation of the isometric relaxation time in hypertensive patients without electrocardiographic signs of myocardial involvement is considered to be a manifestation of latent myocardial involvement as well as of the Q-Ao interval.

When hypertensive patients developed left-sided heart failure, the isometric relaxation time was influenced, showing a tendency to return to a normal range. As discussed in the section on the electromechanical latent time, an elevation of left atrial pressure in congestive heart failure is considered to be responsible for this tendency. As mentioned above, the tension period

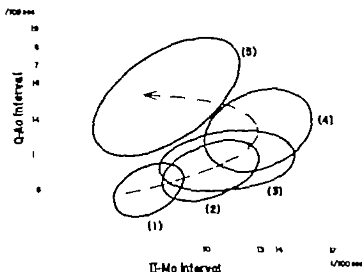


Fig. 12 Changes in the tension period and isometric relaxation time of the left side of the heart in hypertensive cases. The abscissa indicates the duration of the isometric relaxation time the ordinate, the tension period. Rejection ellipses (25 per cent) represent the following conditions (*1*) healthy subjects, (*2*) hypertensive patients without electrocardiographic signs of myocardial involvements, (*3*) hypertensive patients with left ventricular strain pattern or nonspecific ST T abnormalities, (*4*) hypertensive patients both with left ventricular hypertrophy and left ventricular strain pattern or nonspecific ST T abnormalities (*5*) patients with congestive heart failure due to hypertensive heart disease.

was further prolonged in congestive heart failure. In Fig 12 the abscissa and the ordinate refer to the duration of isometric relaxation time and of the tension period respectively A distribution range of cases of each stage from healthy to congestive heart failure is expressed with rejection ellipses of each group (25 per cent) for convenience of description although strictly speaking these stages are not always distinctly separated These findings on the isometric relaxation time and the tension period seemed to shift along the arrow indicated, following a deterioration of the underlaying conditions. When congestive heart failure subsided the findings influenced by it immediately returned to the previous pattern. So in Fig 12 the shift between the area (*5*) and (*4*) or (*3*) might be only an objective sign of fluctuation of the severity of left-sided failure. However a restoration from area (*4*) or (*3*) to area (*2*) or (*1*) was not commonly observed.

In aortic regurgitation the duration of isometric relaxation time was little affected An increased intraventricular blood volume may lead one to assume a delayed opening of the mitral valve but the finding obtained denied this assumption The type of response of the myocardium to a diastolic volume overloading may be quite different from the type of response to a systolic pressure overloading as hypertension.

Summary

The time of occurrence of rapid movements of the heart valves was detected with the ultrasonic Doppler method in cases of hypertension with or without myocardial involvements congestive heart failure resulting from these conditions, and aortic regugitation and then changes in each phase in a cardiac cycle under these conditions were studied

1 The duration of electromechanical latent time is not affected in hypertension without electrocardiographic signs of myocardial involvement but is slightly prolonged in cases of hypertensive heart disease. Changes are more marked in the isometric contraction time than in the electromechanical latent time. The tension period is generally prolonged The isometric relaxation time is markedly prolonged in hypertension especially in cases of left ventricular hypertrophy and strain pattern This prolongation is manifested prior to the changes on the ST T segment.

2 Changes in myocardial conditions secondary to the changes in hemodynamic conditions are possibly more responsible for the above-mentioned changes in the time phase than changes in hemodynamic condition e g high arterial pressure as primary changes.

3 Similar findings are obtained also in cases of arteriosclerotic heart disease

4 Congestive heart failure causes remodifying of changes in the above-mentioned periods. The electromechanical latent time is prolonged and the prolongations of isometric contraction time and of tension period are further deteriorated The prolongation of isometric relaxation time shows a tendency to return to a normal range When congestive heart failure subsides, the above-remodified changes immediately return to the previous pattern

5 In aortic regurgitation the isometric contraction time and the tension period are shortened the isometric relaxation time being little affected It is assumed that the response of the myocardium to a diastolic overloading e.g aortic regurgitation is different from the response to a systolic overloading e.g hypertension.

Addendum I

To examine roles of three factors, i.e. diastolic blood pressure preceding R R interval and myocardial involvements for a prolongation of the Q-Ao interval a regression analysis was employed Regression planes of cases of hypertension without myocardial involvements and those of cases of hypertensive heart disease were shown in three-dimensional space about diastolic pressure the preceding R R interval in the ECG and the Q-Ao interval (Fig 13) The planes were

$$Z = 6.7 + 0.023X + 0.023Y$$

for hypertension without myocardial involvements and

$$Z = 10.8 + 0.027X - 0.004Y$$

for the cases of hypertensive heart disease Here X is diastolic pressure (mm Hg) Y the preceding R R interval (1 100 second) and Z the Q-Ao interval (1 100 second) The difference between these two planes in decline to the Z-axis (the Q-Ao interval) was statistically significant ($p < 0.10$) Also, the partial regression coefficients about the diastolic pressure and about the preceding R R interval did not differ from zero with a statistical significance in cases of hypertensive heart disease ($p > 0.10$ $p > 0.10$) but did in cases of hypertension without myocardial involvement ($0.05 < p < 0.10$ $0.01 < p < 0.05$)

Addendum II

An equation of the regression plane about the diastolic pressure (X mm Hg) and the preceding R R interval (Y 1/100 second) and the II Mo interval (Z 1/100 second) was as follows

$$Z = 4.3 + 0.037X + 0.033Y$$

for cases without myocardial involvement, and

$$Z = 5.4 + 0.037X + 0.029Y$$

for cases of hypertensive heart disease. It was statistically significant that these two planes were not identical ($p < 0.10$) A regression analysis as performed for the tension period showed that the higher the diastolic pressure and the longer the preceding R R interval the more prolonged the II Mo interval in cases of hypertensive heart disease ($0.01 < p < 0.05$ $0.01 < p < 0.05$) and the longer the preceding R R the more prolonged the II Mo interval in cases of hypertension without myocardial involvement ($p < 0.01$)

Addendum III

In a three-dimensional regression analysis, the two planes, the equations of which were $Z = \alpha + \beta X + \gamma Y$ and $Z = \alpha + \beta' X + \gamma Y$ representing hypertensive heart disease and hypertension without myocardial involvement, respectively as shown in Addendum I were cut across $\bar{Y}$ (a mean value of the preceding R R interval) in parallel with the X axis (Fig 14) Where the absolute value of difference between the planes at $\bar{X}$ (a mean value of diastolic blood pressure) that was $|(\alpha + \beta\bar{X} + \gamma\bar{Y}) - (\alpha + \beta'\bar{X} + \gamma\bar{Y})|$ was larger than a sum of increments of Z yielded on both planes when X shifted from $\bar{X}$ to $\bar{X} + \sigma$

$$|(\alpha + \beta\bar{X} + \gamma\bar{Y}) - (\alpha + \beta'\bar{X} + \gamma\bar{Y})| > |\beta|\sigma + |\beta'|\sigma$$

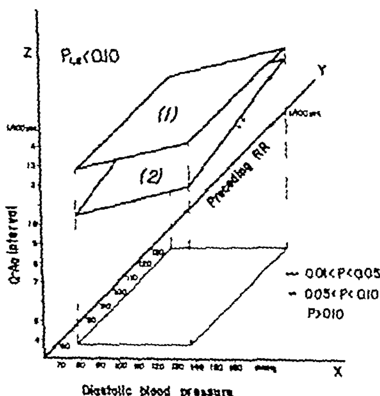


Fig. 13 Comparison between hypertensive patients with and without electrocardiographic signs of myocardial involvements. Regression plane for the tension period (Q-Ao interval) of hypertensive cases ith myocardial involvements (1), and thout myocardial invol ements (2).

Here σ was a standard deviation which had been calculated from the values of diastolic blood pressure at a mean of the preceding R R interval

The same results were obtained on the sectional face at a mean of diastolic blood pressure $\bar{X}$,

$$|(\alpha + \beta\bar{X} + \gamma\bar{Y}) - (\alpha + \beta'\bar{X} + \gamma'\bar{Y})| > |\gamma|\sigma + |\gamma'|\sigma$$

Thus it is meant that a plane of hypertensive heart disease was utterly over a plane of hypertensives without myocardial involvement in a range of over and under the width of standard deviation from a mean value of the preceding R R interval and that of diastolic blood pressure

This result revealed that myocardial nvolvement was the most influential factor for a prolongation of the Q-Ao interval or the II Mo interval, not without a certain

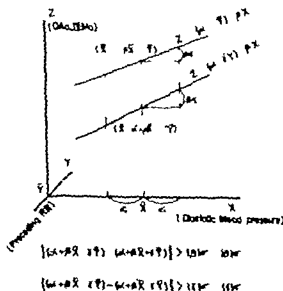


Fig. 14 See elated text.

2. Changes in myocardial conditions secondary to the changes in hemodynamic conditions are possibly more responsible for the above mentioned changes in the time phase than changes in hemodynamic condition e.g. high arterial pressure as primary changes.

3. Similar findings are obtained also in cases of arteriosclerotic heart disease.

4. Congestive heart failure causes remodifying of changes in the above mentioned periods. The electromechanical latent time is prolonged and the prolongations of isometric contraction time and of tension period are further deteriorated. The prolongation of isometric relaxation time shows a tendency to return to a normal range. When congestive heart failure subsides, the above remodified changes immediately return to the previous pattern.

5. In aortic regurgitation the isometric contraction time and the tension period are shortened, the isometric relaxation time being little affected. It is assumed that the response of the myocardium to a diastolic overloading, e.g. aortic regurgitation, is different from the response to a systolic overloading, e.g. hypertension.

Addendum I

To examine roles of three factors, i.e. diastolic blood pressure, preceding R R interval, and myocardial involvements, for a prolongation of the Q-Ao interval, a regression analysis was employed. Regression planes of cases of hypertension without myocardial involvements and those of cases of hypertensive heart disease were shown in three-dimensional space about diastolic pressure, the preceding R R interval in the ECG, and the Q-Ao interval (Fig. 13). The planes were

$$Z = 6.7 + 0.023X + 0.023Y$$

for hypertension without myocardial involvements and

$$Z = 10.8 + 0.022X - 0.004Y$$

for the cases of hypertensive heart disease. Here X is diastolic pressure (mm Hg), Y the preceding R R interval (1/100 second) and Z the Q-Ao interval (1/100 second). The difference between these two planes in decline to the Z axis (the Q-Ao interval) was statistically significant ($p < 0.10$). Also the partial regression coefficients about the diastolic pressure and about the preceding R R interval did not differ from zero with a statistical significance in cases of hypertensive heart disease ($p > 0.10$, $p > 0.10$) but did in cases of hypertension without myocardial involvement ($0.05 < p < 0.10$, $0.01 < p < 0.05$).

Addendum II

An equation of the regression plane about the diastolic pressure (X, mm Hg) and the preceding R R interval (Y, 1/100 second) and the II Mo interval (Z, 1/100 second) was as follows

$$Z = 4.3 + 0.037X + 0.033Y$$

for cases without myocardial involvement, and

$$Z = 5.4 + 0.037X + 0.029Y$$

for cases of hypertensive heart disease. It was statistically significant that these two planes were not identical ($p < 0.10$). A regression analysis as performed for the tension period showed that the higher the diastolic pressure and the longer the preceding R R interval, the more prolonged the II Mo interval in cases of hypertensive heart disease ($0.01 < p < 0.05$, $0.01 < p < 0.05$) and the longer the preceding R R, the more prolonged the II Mo interval in cases of hypertension without myocardial involvement ($p < 0.01$).

Addendum III

In a three-dimensional regression analysis, the two planes, the equations of which were $Z = \alpha + \beta X + \gamma Y$ and $Z = \alpha' + \beta' X + \gamma' Y$, representing hypertensive heart disease and hypertension without myocardial involvement, respectively, as shown in Addendum I, were cut across $\bar{Y}$ (a mean value of the preceding R R interval) in parallel with the X axis (Fig. 14). Where the absolute value of difference between the planes at $\bar{X}$ (a mean value of diastolic blood pressure), that was $|(\alpha + \beta\bar{X} + \gamma\bar{Y}) - (\alpha' + \beta'\bar{X} + \gamma'\bar{Y})|$, was larger than a sum of increments of Z yielded on both planes when X shifted from $\bar{X}$ to $\bar{X} + \epsilon$:

$$|(\alpha + \beta\bar{X} + \gamma\bar{Y}) - (\alpha' + \beta'\bar{X} + \gamma'\bar{Y})| > |\beta|\epsilon + |\beta'|\epsilon$$

ume of the heart, Am. Heart J 54:801 1957
32. Wallace A. G., Mitchell, J H Skinner N S., and Sarnoff S. J Duration of the phases of left ventricular systole Circulation Res. 12:611 1963
33 Sambhi, M P The isometric period of contraction as determinant of cardiac performance and digitalis action, Am. J Cardiol. 6 1042, 1960.
34. Moscovitz, H L and Wilder R. J The pressure events of the cardiac cycle in the dog: Aortic valve lesions, Am. Heart J 54:572, 1957
35 Harrison, T R Coghlan, C and Prieto, G. Movements of the heart during ejection Am. Heart J 62:804, 1961
36. Lange, E. F Einfluss der Pulsfrequenz auf die Kontraktionsphasen des Herzens Ztschr Kreislaufforsch 54:479 1965.
37 Mitsuo, H Analysis of cardiac cycle on the left side of the heart in the left ventricular over loading and damage with the ultrasonic Doppler method (in Japanese) M J Osaka Univ 16 127 1964
38. Simonson E., and Nakagawa, K. Effect of age on pulse wave velocity and aortic ejection time in healthy man and in man with coronary artery disease, Circulation 22 126, 1960
39 Hashimoto, H. Clinical study on latent heart failure, J p Circul J 29 1303 1965
40 Müllahn, H. P Untersuchungen zur Frage der Kontraktilität und des Tonus des Herzens im Jugendalter Ztschr Kreislaufforsch. 54:440, 1965.
41 Mitchell, J H., Linden, R J and Sarnoff S J Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length, Circulation Res. 8 1100, 1960.

Electrical conductivity method for estimating right ventricular output and mathematical model

Robert F. Maronde, M.D.
*Wallace Frasher, M.D.***
*Chester Hyman, Ph.D.**
*Sidney S. Sobin, M.D.*****
Los Angeles, Calif.

When an indicator is injected at a constant rate into a peripheral vein and sampled from a peripheral artery significant recirculation occurs during the time required for the indicator to reach an equilibrium with arterial blood. Consequently an equilibrium plateau usually cannot be detected. If indicator is injected at a constant rate into the right ventricle or pulmonary artery and sampled from the radial artery a brief equilibrium plateau may be achieved.[1] Howard and co-workers[2] realized that the smaller the total volume of blood between the injection and sampling sites the greater the likelihood and duration of the equilibrium plateau. Subsequently Peterson and associates[3] injected T 1824 dye at a constant rate near the aortic valves of dogs and sampled from the lower portion of the aorta, and an equilibrium plateau of the indicator blood mixture of 8 to 10 seconds duration resulted.

Preliminary reports from this laboratory have been published pertaining to a dilution technique that employs the constant rate injection of 5 per cent NaCl solution at the right atrial–inferior caval junction of normal dogs, with sampling from the main pulmonary artery by measurements of changes in electrical conductivity of blood.[4,5] With this technique, the concentration of indicator in main pulmonary arterial blood reaches an equilibrium plateau that lasts 12 to 20 seconds, if the right ventricular output is relatively stable. Under these conditions the relationship of indicator concentration in blood ejected from the right ventricle ascends to the equilibrium plateau as a step function dependent upon the ratio of minimal to maximal right ventricular volumes and

From the Department of Medicine and Los Angeles County Heart Association, Cardiovascular Research Laboratory, University of Southern California School of Medicine, Los Angeles, Calif.
Supported by Grant 335, Los Angeles County Heart Association and Santa Barbara County Heart Association.
Received for publication Jan. 26, 1967.
*Associate Professor of Medicine and Pharmacology. Address: University of Southern California, School of Medicine, 2025 Zonal Ave., Los Angeles, Calif. 90033.
**Associate Professor of Physiology.
***Burley Professor of Investigative Dermatology.
****Professor of Physiology, Department of Physiology, University of Southern California School of Medicine.

the heart rate. In the present study this relationship was evaluated and a mathematical model constructed Comparisons of experimental data with theoretical values predicted by application of this model were made. Also the method under study was correlated with mean and phasic flow measurements from the main pulmonary artery obtained by electromagnetic flow transducers in open chest animals. Examples of the effects of changing output states associated with intermittent positive pressure breathing (IPPB) and spontaneous breathing upon the indicator blood curves will be presented

Methods

Experiments were carried out on 10 closed-chest and 3 open-chest mongrel dogs weighing 15 1 to 23.2 kilograms (average 19 4 kilograms) Intravenous sodium pentobarbital 25 mg per kilogram was used for anesthesia. Tracheotomy and endotracheal intubation were performed and respiration was supported by IPPB (Bird respirator) in all animals. An F8 Holt single lumen electrical conductivity catheter[7] was directed into the pulmonary artery An infusion catheter was advanced to the right atrial-inferior caval junction. In the 10 closed-chest animals an additional infusion catheter was advanced into the right ventricular cavity The catheter tip positions were confirmed at necropsy Intravenous heparin 2.5 mg per kilogram was administered to all animals. If the electrical current was applied to the catheter while the catheter tip was within the ventricular cavity ventricular arrhythmias were frequently encountered If the catheter tip was in the pulmonary artery this was never a problem.

Cannulas were introduced into the left carotid artery and advanced to the aortic arch for measurements of blood pressure Respirations were recorded from pressure fluctuations in a sidearm of the endotracheal tube. During electrical conductivity measurements, blood was drawn through the conductivity catheter at a constant rate approximating 15 ml. per

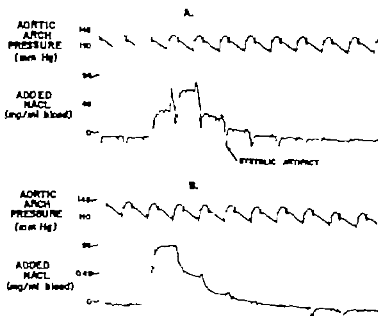


Fig 1 A Ventricular injection. Pulmonary arterial electrical conductivity curve resulting from the single injection of 0 5 ml. of 5 per cent NaCl within the right ventricular cavity I this particular instance, the maximum concentration was not achieved by the first diastolic plateau because the injection extended into two cardiac cycles. The systolic artifact discussed in the text is evident. B Atrial injection. Pulmonary arterial electrical conductivity curve resulting from the single injection of 0.5 ml. of 5 per cent NaCl solution at the right atrial-inferior caval junction in the same animal.

minute for periods of 12 to 180 seconds. With this technique it is possible to measure changes in NaCl content in the blood of the sampled vessel nearly instantaneously.[7] The methods of measurement of conductivity and of calibration of the conductivity changes were similar to that reported by Holt for the measurement of the residual fraction of ventricular blood.

To assess the washout of indicator from the right atrium the 10 closed-chest animals were briefly hyperventilated by IPPB. Ventilation was then temporarily discontinued and a series of single injections of 0.2 to 0.5 ml. of 5 per cent NaCl was administered at the right atrial–inferior caval junction from weighed syringes. Similar injections were administered into the right ventricular cavity. Constant rate injections at the right atrial–inferior caval junction of 8 to 30 seconds duration were interspersed with the single injections. The evaluation of right atrial washout of indicator with this technique is fully treated under Theoretical Considerations (see below).

With the constant rate injection (0.12 to 0.52 ml. per second) of 5 per cent NaCl, right ventricular output was estimated from the equilibrium plateau of the resultant electrical conductivity curve in pulmonary arterial blood. If this curve was unstable as the result of changing flow states associated with respiration, the area under the curve was determined by planimetry. Either the height of the stable equilibrium plateau or the mean area of an unstable curve was converted to milligrams of added NaCl per milliliter of blood and the right ventricular output estimated by use of the Stewart-Hamilton formula.[8]

A systolic artifact similar to that reported by Holt,[7] was frequently recorded (Fig. 1). The exact nature of the artifact is unknown but it introduces no great error in the method. In our experience the appearance of this artifact was inconstant.

In the three open-chest animals, electromagnetic flow transducers were placed around the pulmonary artery. These transducers fit the artery snugly without producing undue constriction. The sampling tip of the conductivity catheter was distal to the flow transducer. This flowmeter has been previously described.[9] A zero flow base line may be obtained by deenergizing the magnet without mechanically occluding the vessel. The difference in the electrical and mechanical zero in vitro does not exceed 1 per cent.[10] There was no significant difference between electrical and the mechanical zero flow reference in our studies. The flowmeter was calibrated in vitro with the use of the animal's blood and was accurate to within ± 10 per cent. Comparisons of mean and phasic flowmeter measurements with right ventricular output estimates could not be carried out simultaneously because of electrical interaction of the conductivity catheter and the flow transducer. However, 12 directly sequential comparisons of the mean pulmonary artery flow mean right ventricle output and estimated by the conductivity method were obtained in 3 animals. It was also possible to compare brief mean decreases in pulmonary artery flow measured electromagnetically as phasic flow with right ventricular output changes associated with IPPB as measured by the conductivity method.

Theoretical considerations

When a single bolus of indicator is introduced during diastole into the ventricular cavity during a steady state and mixing of the indicator with ventricular blood is complete, the concentration curve of indicator blood mixture leaving the ventricle is expressed by the formula

$$C_n = (a/V_d)\,(V_s/V_d)^{n-1} \qquad (1)$$

where

- C_n is the concentration of indicator expressed as milligram per milliliter of blood at heart beat n following the introduction of the indicator,
- a is the quantity of indicator introduced expressed in milligrams,
- V_s is the right ventricular end systolic volume expressed in milliliters, and
- V_d is the right ventricular end diastolic volume expressed in milliliters.

Formula (1) is similar to that of Model 4 of Newman and associates.[1] If V_s and V_d are held constant, the C_{n+1}/C_n ratios are constant and this ratio would equal V_s/V_d, the residual fraction of the

ventricular blood.[7] When the introduction of the indicator extends into more than one ventricular diastolic period and V and V_d are variable, the concentration curve of the indicator blood mixture ejected from the ventricle is expressed by the continuing fraction

$$C = \frac{a}{V_{d_n}} V \; + \qquad (2)$$

$$\frac{\qquad\qquad}{\frac{V_{d_1}}{V_d}\qquad\qquad} V \; +$$

Where

a is the amount of indicator in mg introduced into the ventricle at heart beat n

When V_s/V_d is constant then formula (2) can be expressed

$$C_n = \frac{1}{V_{d_n}}\left[a \left(\frac{V_s}{V_d}\right)^{-} + a \left(\frac{V}{V_d}\right)^{-} \qquad (3)$$

$$+ a_s \left(\frac{V_s}{V_d}\right)^{-} + \ldots a_n \right]$$

Formula (3) demonstrates that C will not decline at a geometric rate i.e. C_{+1}/C will not be constant until a = 0. This is equivalent to complete washout of indicator from the atrium. The subsequent washout of indicator from the ventricle to the pulmonary artery is then the same as that of a single intraventricular injection. When indicator is injected at the right atrial—inferior caval junction the washout of indicator from the atrium into the ventricle equals a in Formula (3) and C_{+1}/C ratios of the pulmonary artery curves that result from the introduction of a single indicator bolus into the atrium and a single indicator bolus into the ventricle will be similar and may be used to assess the atrial washout of indicator from the atrium. In the 10 closed-chest animals 67 curves that resulted from single intra atrial injections of 5 per cent NaCl and 73 curves that resulted from single intraventricular injections were recorded. A total of 332 C_{+1}/C ratios were placed into three subgroups (1) C_2/C_1 when $C_1 = C_{max}$ (2) C_3/C_2 (3) C/C_3 C_{+1}/C. The mean $\bar{x}$ and the mean standard deviation $\bar{s}$, were calculated for each subgroup containing N number of ratios. These are presented in Table I. Examples of the curves obtained with single intra atrial and intraventricular injections of 5 per cent NaCl are shown in Fig. 1.

There was no statistically significant difference between these subgroup means. Excessive variation of the C_2/C_1 ratios resulted in a high value of $\bar{s}$ for the C_2/C subgroup. The major contribution to this high value was the result of four of 32 C_2/C ratios with intra atrial injection of indicator and three of 35 C_2/C ratios with intraventricular injection that fell outside the 99 per cent level of confidence from the mean of their respective C_2/C_1 subgroup. The excessive variation in the C_2/C ratios

Table I. Comparison of the mean $\bar{x}$ and the average standard deviation $\bar{s}$ for comparable subgroups of the C_{n+1}/C ratios recorded from the pulmonary arterial pulse number-concentration curves that resulted from a single intra-atrial or intraventricular injection of 5 per cent NaCl solution

Ratio	Injection site: Atrium			Ventricle		
		N			N	
C_n/C_{n-1} C $_{+1}/C_n$	0 62	53	±0 05	0 56	72	±0 05
C_3/C	0 55	67	±0 06	0 55	73	±0 06
C_2/C	0 51	32	±0 10	0 54	35	±0 14

may result from (1) the extension of the indicator injection into the subsequent ventricular diastolic period (2) variable mixing of the indicator with blood during the initial cardiac cycle (3) regurgitation of indicator from the ventricle into the atrium. Holt[7] has demonstrated that regurgitation of indicator under these conditions, condition (3) above averaged 2 per cent. This small degree of regurgitation would not result in this excessive variation of the C_2/C_1 ratios Because this variation of the C_2/C_1 ratios was found after both intra atrial and intraventricular single injections, it was believed that condition (2) above variable mixing of the indicator was not operative Condition (1) extension of the indicator injection into the second diastolic period would occur inconstantly when the injection was random in relation to the cardiac cycle and this was interpreted as the cause of the variation of the C_2 C_1 ratios. Therefore the analysis of the C_{n+1}/C_n ratios indicated that the indicator bolus cleared the right atrium in one cardiac cycle under the conditions of the experiment. With this assumption, a mathematical model was constructed by modifying Formula (3) to apply to the pulmonary artery curves that resulted from the constant rate injection of indicator at the right atrial–inferior caval junction. Formula (4) expresses this relationship

$$C = \frac{cq}{V_{d_n}}\left[\Delta t_1 \frac{V_{e_1} V_{e_2} \cdots V_{e_{n-1}}}{V_{d_1} V_{d_2} \cdots V_{d_{n-1}}} + \Delta t_2 \frac{V_{e_2} V_{e_3} \cdots V_{e_{n-1}}}{V_{d_2} V_{d_3} \cdots V_{d_{n-1}}} + \Delta t_3 \frac{V_{e_3} V_{e_4} \cdots V_{e_{n-1}}}{V_{d_3} V_{d_4} \cdots V_{d_{n-1}}} \cdots + \Delta t_n\right] \quad (4)$$

where

- c is the concentration of indicator expressed as milligrams per milliliter
- q is the flow rate of indicator expressed as milliliter per second and
- Δt_n is the duration of the cardiac cycle in seconds at heart beat n after initiation of the constant rate injection.

Under steady conditions, V_e, V_d and Δt are constant Formula (4) then may be expressed

$$C = \frac{cq\,\Delta t}{V_d} \sum (V_e/V_d)^{n-1} \quad (5)$$

The analytic limit of Formula (6) is

$$C_{n \to \infty} = \frac{cq\,\Delta t}{V_d}\,\frac{1}{1 - V_e/V_d} \quad (6)$$

The ascending limb of 56 constant rate injection curves recorded while ventilation was suppressed consisted of a series of steplike ascents (Fig 2) If the terms of

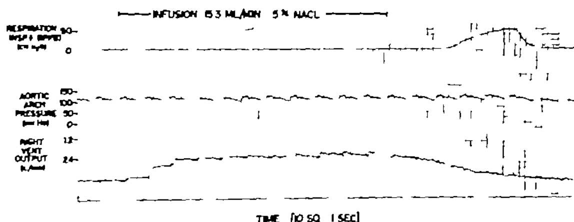


Fig 2 Right ventricular output as measured by the pulmonary arterial electrical conductivity curve that resulted from the constant-rate injection of 5 per cent NaCl solution at the right atrial–inferior caval junction during a period when ventilation was suppressed The residual fraction of the right ventricle, as estimated from single injection curves, was 0.33 (not shown).

Formula (5) are known the rate of ascent to the equilibrium plateau recorded may be tested against the theoretical value predicted by Formula (5) For this purpose the term V_r/V_d was determined from the C_{n+1}/C_n ratios of the descending limbs of the pulse number-concentration curves that resulted from the single intra-atrial and intraventricular injections of 5 per cent NaCl and V_d was calculated in the manner described by Holt by use of the formula

$$V_d = \frac{s\,o}{1 - V_r/V_d} \qquad (7)$$

where s o is the stroke output of the right ventricle in milliliters.

Determined from the minute output estimated by the constant rate injection technique and the heart rate.

Because the constant-rate injection of NaCl solution was initiated in a random manner in regard to the cardiac cycle the concentration reached during the interval Δt_1 of Formula (4) would infrequently be of the same magnitude as Δt Δt Therefore even under steady conditions c q Δt could not be assumed to be constant until c q Δt_1 was reached. For the purposes of testing the experimental data against the theoretical values derived from Formula (4) the values for c q $\Delta t_1/V_d$ found experimentally were used and the theoretical values for c q $\Delta t_a/V_d(V_r/V_d)$ starting with Δt_2 were added to c q $\Delta t_1/V_d$ $(V_r/V_d)^{n-1}$ The experimental values for C_2, C_3, and C_4 were then expressed as percentages of the equilibrium plateau and compared to the theoretical values for each C_1 C_n subgroup.

Results

In the 10 closed-chest animals, 56 of 69 constant rate injection electrical conductivity curves were recorded from the pulmonary artery during periods of suppressed ventilation. A stable equilibrium plateau was achieved in each instance. The ascending limbs of these 56 curves rose in a steplike fashion with each heart beat representing C of Formula (4) to the equilibrium plateau The mean of the theoretical values for the C_2, C_3, and C subgroups of the ascending limb expressed as percentages of the equilibrium plateau were 67.2 84.1 and 91 8 per cent respectively The mean of the experimental values recorded for the same C subgroups were in close accord with the values predicted from the mathematical model and these means and their mean standard deviations were 65 9 ± 1 9 85 0 ± 1.3 and 90 9 ± 1 6 per cent respectively

In Fig 2 a photograph of a representa

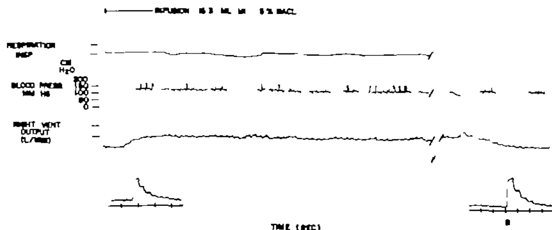


Fig 3 Right ventricular output as measured by the pulmonary arterial, electrical conductivity curve that resulted from 30 second constant-rate injection of 5 per cent NaCl solution at the right manifests itself as a slight rise in the latter half of the plateau A 10 second segment has been removed to permit more detailed reproduction. *A* and *B* are single injection curves (injection site right atrial-inferior caval junction) recorded before and subsequent to the constant-rate injection curve. Respiration was suppressed by brief period of hyperventilation preceding the infusion.

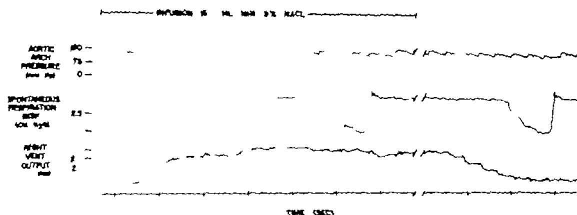


Fig 4 Right ventricular output as measured by the electrical conductivity curve of pulmonary arterial blood recorded during the constant-rate injection of 5 per cent NaCl solution at the right atrial–inferior caval junction The unstable plateau is associated with spontaneous respiration. The mean area of the curve, obtained by planimetry was converted to milligrams of added NaCl per milliliter of blood for the purpose of estimating right ventricular output. An 8 second strip of the record was not included to enhance detailed reproduction

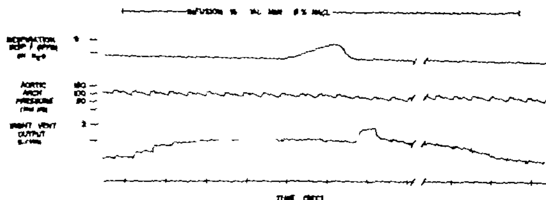


Fig 5 Right ventricular output as measured by the electrical conductivity curve of pulmonary arterial blood resulting from the constant-rate injection of 5 per cent NaCl solution A brief decrease in right ventricular output associated with IPPB was recorded. A 4 second segment has been removed to insure better reproduction

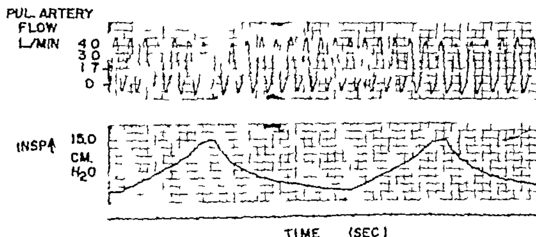


Fig 6 Phasic flow in the main pulmonary artery recorded by the electromagnetic flowmeter A decrease in flow associated with IPPB was recorded by this technique as well as by the constant-rate injection method as shown in Fig 5.

tive record of an electrical conductivity curve that resulted from the constant rate injection of 5 per cent NaCl solution at the right atrial-inferior caval junction is presented Recirculation was usually evident if the constant-rate injection was continued for as long as 20 seconds, and at the end of 30 seconds recirculation increased the plateau height by as much as 30 per cent (Fig 3)

The right ventricular output estimates calculated from the 69 constant rate injection curves averaged 0 12 L. per kilogram per minute with a mean standard deviation for each group of measurements obtained from a specific animal of ± 6 6 per cent. Twenty-one of the 69 curves represented directly sequential measurements and the mean standard deviation of these 21 test re-test measurements was ± 3 6 per cent.

The indicator-blood curves recorded with the constant rate injection technique in the presence of spontaneous breathing and IPPB did not exhibit a stable concentration plateau (Fig 4) However if the respiratory rate was slow e.g less than 12 per minute an initial plateau could usually be achieved and a stable inter respiratory plateau was evident. Under these conditions an increase in output was recorded during spontaneous respiration and a brief decrease in output was recorded following IPPB (Fig 5)

In the 3 open-chest animals, the phasic flow recorded by the electromagnetic flowmeter from the pulmonary artery showed a decrease in flow with IPPB (Fig 6) This decrease appeared slightly earlier in the respiratory cycle than that recorded with the constant rate injection technique.

Comparison of mean flow determinations in contrast to phasic flow by the 2 methods showed good agreement of the averages, although individual comparisons varied by as much as 20 per cent The mean of the 12 output estimates by the constant rate injection method was 1.50 L. per minute and for the mean flow measurements by the flowmeter averaged 1.52 L. per minute. The average decrease

Table II The right ventricular output estimates by the constant rate injection method and the mean flows in the main pulmonary arterial recorded by the electromagnetic flow transducer are compared. The decrease in pulmonary artery flow and right ventricular output associated with IPPB are also tabulated There were 12 sequential determinations with each method.

Dog N	Wt. (Kg)	Flowmeter		Constant rate injection	
		Mean Flow (L/min)	Average decrease (IPPB) (L/min.)	Output (L/min)	Average decrease (IPPB) (L/min)
1	15	1 33	0 16	1 20	0 16
		1 32	0 22	1 49	0 30
		1 30	0 27	1 55	0 21
		1 10	0 15	1 12	0 14
		1 25	0 20	1 15	0 23
2	17	1 70	0 31	1 79	0 28
		1 89	0 36	1 70	0 26
		1 80	0 29	1 53	0 32
3	19	1 6_	0 12	1 62	0 19
		1 70	0 22	1 42	0 22
		1 61	0 34	1 79	0 29
		1 61	0 25	1 75	0 23
Averages	17	1 52	0 24	1 50	0 23

associated with IPPB as estimated by the 2 methods also was in satisfactory agreement (Table II).

Discussion

When a changing flow state exists, maximum changes in output in contrast to mean changes, would not be accurately reflected by the indicator-blood curve until a new steady state existed for at least a few heart beats. This theoretically (Formula 4) may require no more than 3 to 8 heart beats unless the ratio of V_r/V_d exceeds 0.7. When output changes occur after an equilibrium plateau has been established and there is a return to the pre-existing equilibrium plateau, it would be valid to estimate mean changes in output from this curve, even though the change was not of sufficient duration to reflect the maximum change accurately.

With the constant rate injection of 5 per cent NaCl solution at the right atrial–inferior caval junction, the rate of ascent of the resultant indicator-blood concentration curve to a stable equilibrium plateau was in good agreement with the theoretical values predicted by Formula (4).

The close agreement between the C_{n+1}/C_n ratios obtained with the single right atrial–inferior caval junction and intraventricular injections supports the validity of Holt's method.[7] It would be a remarkable coincidence to have irregular intraventricular distribution of indicator with these two injection techniques that could be reflected consistently by the resultant indicator-blood concentration curves as similar values for the residual fraction.

With indicator-dilution techniques for the estimation of cardiac output the basis of most mathematical models that have been proposed to express the relationship of indicator concentration in the blood at the sampling site has been

$$C_n = \left(\frac{c\dot{q}\,\Delta t}{V_d}\,\frac{1}{1 - V_r/V_d}\right) - \left(\frac{c q\,\Delta t}{V_d}\,\frac{1}{V_r/V_d}\right) e^{-\frac{n q}{V_d}} \qquad (7)$$

where e is the natural log base 2.718.

Although the analytic limit of this formula is the same as Formula (5), the two formulas represent different mathe-

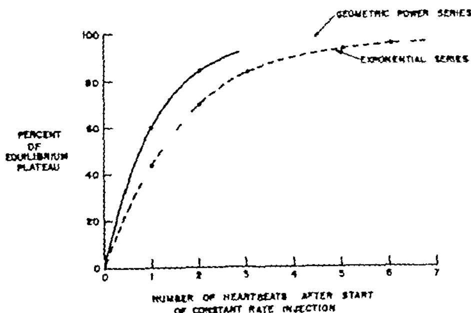


Fig. 7. Theoretical rate of ascent of indicator-blood concentration curves for the same stroke output and residual fraction of ventricular blood using Formula (5) representing the geometric power series (solid line) and Formula (7) representing the exponential series (broken lines).

matical series. Formula (5) is the geometric power series

$$\frac{1}{1-x} = 1 - x + \frac{x}{2} - \frac{x}{3} + \frac{x}{4} - \frac{x}{5} \qquad (8)$$

The rate at which these two series converge toward their analytic limit, i.e., the equilibrium plateau, may vary significantly (Fig. 7). The relevance of ascertaining which, if either, series represents the ascent to the equilibrium plateau may be questioned, particularly in view of the confines of the limited conditions imposed by the present experimental methods. However, the development of the indicator dilution cardiac output method has been more on an empiric basis and, as pointed out by Dow,[12] mathematical models have had little relevance or agreement to data obtained by the practical application of the method. We are of the opinion that if a biologic system can be defined in mathematical terms, even within narrow limits, an initial step toward more complete definition has been taken and therefore is of importance.

Summary

A constant-rate injection dilution technique for estimating right ventricular output was employed in normal dogs. Five per cent NaCl solution was injected at the right atrial–inferior vena caval junction and changes in electrical conductivity were measured from pulmonary arterial blood. There was good agreement between right ventricular output estimates with this technique and mean pulmonary arterial flow measured electromagnetically. Evidence was presented that the added indicator cleared the right atrium within one cardiac cycle under the conditions of the experiment. A mathematical model was constructed to express the relationship of indicator concentration in pulmonary arterial blood to the indicator injection rate, the residual fraction of right ventricular blood, and the heart rate.

REFERENCES

1. Hamilton, W. F., and Remington, J. W.: Comparison of the time-concentration curves in arterial blood of diffusible and non-diffusible substances when injected at a constant rate and when injected instantaneously, Am. J. Physiol. 148:354, 1947.
2. Shepherd, J. T., Bowers, D., and Wood, E. H.: Measurement of cardiac output in man by injection of dye at a constant rate into the right ventricle or pulmonary artery, J. Appl. Physiol. 7:629, 1955.
3. Howard, A. R., Hamilton, W. F., and Dow, P.: Limitations of the continuous infusion method for measuring cardiac output by dye dilution, Am. J. Physiol. 175:173, 1953.
4. Peterson, L. H., Helrich, M., Greene, L., Taylor, C., and Choquette, G.: Measurement of left ventricular output, J. Appl. Physiol. 7:258, 1954.
5. Maronde, R. F., Frasher, W. G., Hyman, C., and Sobin, S. S.: Changes in pulmonary arterial blood flow produced by intermittent positive pressure breathing and a Drinker respirator, 4th European Congress of Cardiology, Prague, pp. 311 (abstr.), 1964.
6. Maronde, R. F., Frasher, W. G., Hyman, C., and Sobin, S. S.: Cardiac output estimated by a constant infusion conductivity method, The Physiologist 7:198, 1964 (abstr.).
7. Holt, J. P.: Estimation of the residual volume of the ventricle of the dog's heart by two indicator dilution techniques, Circulation Res. 4:187, 1956.
8. Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: Studies on the circulation. I. Physiol. and mathematical considerations, Am. J. Physiol. 89:322, 1929.
9. Westersten, A. G., Herrold, G., and Assali, N. S.: A gated sine wave blood flow meter, J. Appl. Physiol. 15:533, 1960.
10. Assali, N. S., Morris, J. A., and Beck, R.: Cardiovascular hemodynamics in the fetal lamb before and after lung expansion, Am. J. Physiol. 208:122, 1965.
11. Newman, E. V., Merrell, M., Genecin, A., Monge, A., Milnor, W. R., and McKeever, W. P.: The dye dilution method for describing the central circulation. An analysis of factors shaping the time concentration curves, Circulation 4:735, 1951.
12. Dow, P.: Estimations of cardiac output and central blood volume by dye dilution, Physiol. Rev. 36:77, 1956.

Pulmonary edema induced by renal extracts originating from rats with experimental hypertension

Teruo Omae, M.D.
Noriaki Hattori, M.D.
Akinobu Sumiyoshi, M.D.
Yasushi Iwata, M.D.
Kenjiro Tanaka, M.D.
Kenzo Tanaka, M.D.
Shibanosuke Katsuki, M.D.
Fukuoka, Japan

The existence of pressor, necrotic, and hemorrhagic principles in the kidney was first postulated by Winternitz and associates. However, vascular injury induced by parenteral administration of renal extract had been, for the most part, attributed to renin initially.[1-4] More recently, Nakao and co-workers described a vascular injury factor that was present in the nonpressor aqueous fraction of *renal cortical extract obtained from ischemic* kidneys of the rabbit. The present study was undertaken primarily to determine a vascular effect of renal extract containing varying amounts of renin originating from rats with experimentally induced hypertension. These extracts were injected *intraperitoneally into bilaterally* nephrectomized rats. This report is concerned with pulmonary edema which occurred with great frequency in these experimental conditions before the development of demonstrable vascular lesions.

Materials and method

A total of 84 male rats of the Wistar King strain, weighing from 144 to 232 grams, were anesthetized with amytal (10 mg. per kilogram of body weight administered intraperitoneally), bilaterally nephrectomized, and injected with renal extract when they recovered from anesthesia. They were divided into five groups according to the types of renal extract *injected. The experiments for each rat* group were performed at one time for Groups I, II, IV, and V. However, rats in Group III were subjected to experimentation at a later time, as were rats which were added to Groups IV and V. The rats were added to Groups IV and V *after obtaining the initial results from the* original number of rats in these groups. The number of rats from all groups were totalled and are included in the figures appearing below.

Group I: clipped kidney (8 rats)

From the Second Department of Internal Medicine and Department of Pathology, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
Received for publication Feb. 2, 1967.
Address: Second Department of Internal Medicine, Faculty of Medicine, Kyushu University, 1276 Katakasu, Fukuoka, Japan.

Group II contralateral kidney to the clipped (9 rats)
Group III kidney from rats given 1 0 per cent saline as drinking fluid (20 rats)
Group IV normal kidney (30 rats) and
Group V 0 9 per cent saline instead of renal extract (17 rats)

Renal extract was made according to the procedure of Gross and Sulser[7] by centrifugation of a mixture of 6 ml. of 0 9 per cent saline and tissue from one kidney ground with sea sand at 10,000 r p m. for 10 minutes at 4 C Aliquots of 4 ml. of the supernatant fluid were injected intraperitoneally into each rat. Pressor activity of each extract was assayed by a pentolinium treated vagotomized rat, anesthetized with amytal the activity was expressed as angiotensin II equivalent per 0 1 ml The kidney which was to be used for the experiments in Group I and II was removed 40 to 60 days after unilateral main renal artery constriction had been performed For Group III 1 0 per cent saline was given as drinking fluid for a period of 24 to 60 days following uninephrectomy or uninephrectomy plus resection of the upper half of the other kidney as performed by Koletsky and Goodsitt. All rats were fed a commercial rat diet, and tap water was available as desired unless otherwise specifically indicated Blood pressure was determined once a week by tail sphygmography and at the time of death it was 180 1 ± 26 4 mm. Hg (mean ± S.D) in the rats with renal artery constriction and 210 ± 30.5 mm. Hg in those given salt together with the reduction of renal mass. After intraperitoneal injection of renal extract the early death rate in each group and the blood chemistry (nonprotein nitrogen [NPN] analysis) in the survivors were determined At autopsy the heart and the lung were removed for weighing and histologic studies. Paraffin sections were stained with hematoxylin and eosin and with periodic acid–Schiff stains. Frozen sections of the lung tissues were stained with a fluoresceinated antibody to rat fibrinogen which cross-reacted immunologically with fibrin Rat fibrinogen of the Wistar King strain for use as an antigen was prepared by a modification of the method of Smith and Yoshinari. About 10 mg of fibrinogen were injected into each of 3 adult male rabbits at weekly intervals for 4 weeks by the multiple intramuscular technique. Freund's adjuvant was used simultaneously Ten days after the last injection the rabbits were bled and the crude rabbit serum tested in the agar gel and cellulose acetate paper diffusion system for the presence of precipitating antibodies. Antibodies to contaminating antigens were repeatedly absorbed by using the serum of the rat until the antiserum formed one precipitation line against the rat plasma in the agar gel diffusion system The gamma globulin of this serum was separated and labeled with fluorescein isothiocyanate by the technique described by Hamashima and Kyogoku[1] This fluorescein-conjugated rabbit antirat fibrinogen was reabsorbed with rabbit liver emulsion to remove any dissociated dye and reduce the chances of nonspecific staining

Rat lung tissue obtained at autopsy was rapidly frozen in n-hexane precooled with a mixture of dry ice and acetone. Sections were cut at 6μ in the cryostat picked up on warm slides, air dried fixed for 2 hours or more with cold (−20° C) 95 per cent ethanol and then stored at −70° C until required for use Staining with fluoresceinated antibody was performed as described by Hamashima and Kyogoku. Staining time was continued overnight at 0 to 4 C As in the control procedures, the absorption technique of the fluorescein-conjugated antibodies with antigen and immunological blocking with nonfluoresceinated antibody were performed.

Results

Early death rate Early death within 15 hours following the injection occurred most frequently in Group I (Table I) Six out of 8 (75 per cent) died in Group I and 33 per cent, 30 per cent 15 per cent and 6 per cent of the rats in Groups II III IV and V respectively The cause of death was most frequently considered to be pulmonary edema because of marked dyspnea before death and of the postmortem findings such as frothy fluid in the airways and marked consolidation of the lungs Blood

*Production of Oriental Yeast Manufacturing Co., Japan

Table I. Mortality rates and clinicopathological findings following injection of various types of renal extract

Group	No. of rats	Rats died within 15 hr		Pressor effect of renal extract injected (ng./0.1 ml. of angiotensin II equiv.)	Body wt. (Gm.)		NPN in survivors (mg./100 ml.)	Lung (mg./Gm. of body wt.)	Heart (mg./Gm. of body wt.)	Pleural effusion (ml.)
		No.	Percent		Before	After				
I	8	6	75	32.8 ±8.2	171.2 ±14.5	176.2 ±12.4	122.3 ±15.2	9.4 ±1.1	3.15 ±0.49	4.9 ±1.3
II	9	3	33	0.4 ±0.1	168.9 ±12.6	165.2 ±13.7	188.0 ±9.0	10.0 ±3.5	3.42 ±0.38	0.6 ±1.0
III	20	6	30	3.6 ±2.4	192.7 ±24.8	192.8 ±19.0	217.2 ±9.5	9.0 ±4.7	3.10 ±0.28	3.1 ±1.0
IV	30	5	15	8.4 ±1.5	167.9 ±21.2	169.1 ±26.3	219.0 ±18.8	8.1 ±3.2	3.27 ±0.61	3.4 ±1.6
V	17	1	6	0	162.8 ±18.5	161.4 ±13.0	227.3 ±41.2	7.4 ±2.0	3.40 ±0.40	0.3 ±0.3

Values indicated are means ± standard deviations.

NPN was 123 ± 15, 188 ± 9, 217 ± 10, 219 ± 19, and 227 ± 41 mg. per 100 ml. in the rats which survived beyond 15 hours from Groups I to V, respectively, from which it was concluded that the early death was not necessarily attributable to renal insufficiency per se. Pressor activity of the renal extract administered was definitely increased in Group I, but significantly decreased in Groups II and III when compared to that in Group IV. It was 32.8 ± 8.2, 0.4 ± 0.1, 3.6 ± 2.4, and 8.4 ± 1.5 ng. per 0.1 ml. of angiotensin II equivalent from Groups I to IV, respectively. Therefore, the early death rate was highest in Group I receiving an extract containing the greatest amount of renin, but it did not correlate with the amount of renin injected because the death rate was higher in Groups II and III than in Group IV.

Autopsy findings. All the animals, whether undergoing early death or put to death by exsanguination between 15 and 22 hours following the injection, were autopsied. Body weight was determined twice, immediately after the injection and at the time of dying or being put to death. It was generally increased in the animals showing fluid retention following the injection. Fluid retention was noted in the pleural and abdominal cavities as well as in the subcutaneous tissue, the degree of which seemed to parallel the amount of renin received. Pleural effusion was most prominent in Group I, followed by Groups IV, III, II, and V in that order. The protein content in pleural effusion was high (between 2.8 and 4.2 Gm. per 100 ml.) and the pattern of its protein fraction was similar to that of serum protein by agar electrophoresis as reported by previous investigators[3,4] (Fig. 1).

Macroscopic findings of the lungs were classified into five groups according to a modification of the description of Lindqvist[12]: −, normal appearance; ±, a few petechiae; +, dotted lung surface; ++, spotted lung surface; and +++, lung with mottled surface or consolidation. As shown in Table II, normal lung surface was not seen in Groups I, II, and III, but was seen in 17 per cent and 24 per cent of Groups IV and V, respectively. The changes of ++ and +++ grades were seen in 100 per cent, 44 per cent, 55 per cent, 37 per cent, and 29 per cent of the rats in Groups I to V, respectively. Severity of the pul-



Fig. 1. Protein patterns (Group IV). *A*, In the serum (total protein 6.8 Gm. per 100 ml.). *B*, In the pleural effusion (total protein 3.6 Gm. per 100 ml.)

Table II. Macroscopic findings of the lung

Group	*Grading*					*Total*
	−	±	+	++	+++	
I	0	0	0	4	4	8
II	0	0	5	1	3	9
III	0	3	6	4	7	20
IV	5	7	7	6	5	30
V	4	2	6	3	2	17

See the text for grading criteria.

monary changes was directly in proportion to the early death rate. Wet weight of the lung per body weight was also heavier in Groups I, II, and III than in IV and V. There was no essential difference of the heart weight among the groups.

Histologic examinations. Protein-rich exudate and hemorrhage were found in the alveolar spaces as well as in the perivascular interstitial connective tissue. The severity of these changes was in general correlated with the macroscopic findings described above. The changes were widespread and very severe, particularly in the rats undergoing early death. The extensive exudation seen in an animal that died after injection of the extract of the salt treated kidney is shown in Fig. 2. In the lungs with marked exudate, edema of the perivascular interstitial connective tissue of relatively large arteries was also noted (Fig. 3). Fibrinoid changes in the arterioles were not seen in any of the rats. Flourescent antibody technique clearly showed leakage of fibrinogen into the perivascular interstitial connective tissue and alveolar spaces (Figs. 4 and 5).

Discussion

Substantial effusion into serous sacs (peritoneum and pleura) was induced by earlier investigators[2-4] by the administra-

tion of crude renal extracts and of preparations of renin into nephrectomized rabbits, rats, and guinea pigs. Asscher and Anson[11] described a vascular permeability factor of renal origin responsible for the serous effusion and arterial necrosis seen in nephrectomized rats injected with renal extract. Whether this factor was independent of renin or not was not mentioned. Since renin preparation is not homogeneous, the nature of the contaminants of the preparation, the route of administration, and the species difference of animals should always be taken into account before any conclusion is drawn from the experiments as to whether renin or other renal factors were involved in pathogenesis of hypertensive vascular disease. Pulmonary edema, however, has not been reported in the animals treated with renal extracts except for the descriptions of Nairn[3] and Nairn and colleagues. They noticed that small focal hemorrhages in the lungs frequently occurred in the nephrectomized animals injected with crude extracts of normal kidneys. But no evidence was presented to indicate that plasma leakage occurred elsewhere than in the serous cavities.

Pulmonary edema rather frequently occurs in various forms of renal disease such as uremic pulmonary edema, uremic lung, uremic pneumonitis, etc. Toxic substances that cause an increase in capillary permeability were also incriminated in uremia.[12] Since all the test rats were nephrectomized bilaterally in the present series, it would appear that in light of the above, the situation would provide a milieu in which the rats would be particularly susceptible to pulmonary edema. Several other conditions known to predispose to pulmonary edema were also provided: overhydration due to fluid administration into peritoneal cavity and administration of renal extract

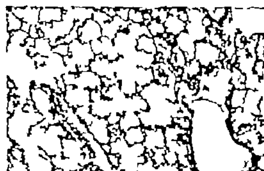


Fig. 2. Extensive extravasation of protein-rich materials in alveolar spaces (Group III). (Hematoxylin and eosin; original magnification ×157.)



Fig. 3. Pulmonary edema and edema of the perivascular interstitial connective tissue with dilated lymphatic spaces (Group III). (Hematoxylin and eosin; original magnification ×157.)

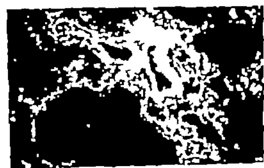


Fig. 4. Fibrinogen and/or fibrin in perivascular connective tissue and alveolar spaces (Group IV) by fluorescent antibody technique. (Original magnification ×180.)

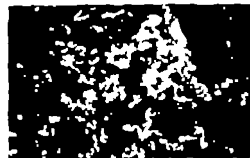


Fig. 5. Fibrinogen and/or fibrin in alveolar spaces (Group I), by fluorescent antibody technique. (Original magnification × 360.)

which will increase blood pressure and/or vascular permeability Since many of the nephrectomized rats were dying rather soon after administration of the extracts of kidney tissue a period of 15 hours was settled upon arbitrarily for determining the early death rate not directly related to uremia, and, to protect the lungs from postmortem changes, the rats having survived beyond this period were killed.

Serous effusion was more markedly advanced in Group I given the extract of clipped kidney when compared with that in Group IV with normal kidneys ($p < 0.02$) but significantly less pronounced in Group II given the extract of contralateral kidney to the clipped ($p < 0.001$) The early death rate was highest in Group I it was also higher in Groups II and III given the extract of salt treated kidney than in Group IV In accord with the report of Gross and co-workers,[12] the renin content was increased in the clipped kidney but significantly decreased in the contralateral kidney to the clipped and also in salt treated kidney The early death was attributable to pulmonary edema in most of the test rats and will be noted later Ascher and Anson[11] performed more or less the same types of experiments in rats, but they did not note pulmonary edema presumably because they merely used extracts of normal kidneys. A permeability factor of renal origin has generally been accepted as causing effusion into serous sacs,[1-11] and/or the proteinuric effect due to increased glomerular permeability This factor has been considered as closely linked to the pathogenesis of hypertensive vascular disease[1,11] but whether or not it is identical with renin has not been determined conclusively Some observations, however suggest that it is, at least in part independent of the pressor activity of renin. [13] In this regard Masson and associates[14] concluded that crude renin is more active than semipurified renin in producing vascular disease because of the more prolonged action of renin due to retarded resorption

The cause of death in our test animals was not renal insufficiency per se but pulmonary edema. Clinical signs and macroscopic as well as microscopic examinations of the lungs were consistent with the diagnosis of pulmonary edema Although separation of active principle(s) from renin which cause serous effusion or pulmonary edema could not be made successfully under the present experimental conditions, it is worth noting that pulmonary edema was induced more frequently in the animals injected with the renal extracts originating from hypertensive animals than in those similarly treated with normal kidney extracts, even when the extracts contained a significantly less amount of renin The fact that the incidence of early death due to severe pulmonary changes was highest in those given clipped kidney extracts containing a large amount of renin suggests two possible mechanisms, i.e. renin itself has a property of increasing vascular permeability or its pressor action works as an accelerating or predisposing factor of pulmonary edema.

Summary

In an attempt to elucidate a vascular injury factor of renal origin in relation to renin renal extracts of varying renin content originating from rats with experimental hypertension were injected intraperitoneally into bilaterally nephrectomized rats. Experimental hypertension was produced by unilateral main renal artery constriction and also by salt ingestion associated with uninephrectomy or uninephrectomy plus resection of the half of the remaining kidney Renin content was increased in the extract of clipped kidney but much less in the extracts of the kidney contralateral to the clipped and also of the salt treated kidney Early death within 15 hours following the injection occurred more frequently in the rats given the extracts of three types of hypertensive kidneys than in those similarly treated with the extract of normal kidney The extract of clipped kidney was most injurious of all. The major cause of death was considered to be pulmonary edema. The significance of these findings was discussed.

REFERENCES

1. Winternitz, M. C., Mylon, E., Waters, L. L., and Katzenstein, R. Studies on the relation of the kidney to cardiovascular disease, Yale J Biol. & Med. 16:623 1940.
2. Nairn, R. C Edema induced in the rabbit by

infarction of the kidneys and by the injection of renal extracts after nephrectomy J Path. & Bact. 67:537 1954

3 Sellers, A. L. Smith S III Marmorston, J and Goodman, H C Studies on mechanism of experimental proteinuria, J Exper Med 96:643 1952.

4 Nairn, R. C Masson, G M C and Corcoran, A C The production of serous effusion in nephrectomized animals by the administration of renal extract and renin, J Path & Bact 73 155 1956.

5 Masson, G. M C Kashii Ch M tsunaga, M and Page, I H. Hypertensive vascular disease induced by heterologous renin, Circulation Res. 18:219 1966.

6. Nakao, K Ikeda, M Fujii, J Terasaw a, F Kurihara, H. Kimata, S Matsushita, S., and Yamaguchi, H. Acute vascular lesions produced by selected non-pressor renal cortical extracts, Jap. Circulation J 30:539 1966

7 Gross, F and Sober F Wirkungsverstarkung von Renin und Nierenextrakt and der nierenlosen Ratte Arch. exper Path. & Pharmakol 229:338, 1956

8. Koletsky S. and Goodsitt A. M N tural history and pathogenesis of renal ablation hypertension, Arch. Path. 69:654 1960.

9 Yoshinari, M The mechanism of blood coagulation, J Kyu. Hem. Soc. 4 107 1954 (in Japanese)

10 Hamashima, Y and Kyogoku, M : Immunology, ed. 1 Tokyo, J pan, 1965 Igaku Shoin Ltd (in J panese)

11 Ascher A. W and Anson, S. G.: A vascular permeability factor of renal origin, Nature 198 1097 1963.

12 Lindqvist, B Experimental uremic pulmonary oedema, Acta med. scandinav Suppl. 418 1964.

13 Gross, F Schaechtelin, G. Brunner H and Peters, G. The role of the renin-angiotensin system in blood pressure regulation and kidney function, Canad. M A. J 90:258, 1964

14 Lippman, R. W Green, H J and Oliver J Mechanism of proteinuria. IV Effect of renin on hemoglobin excretion, J Exper Med 93:605 1951

15 Paldino, R. L., and Hyman, C Mechanism whereby renin increases the rate of T 1824 disappearance from the circulation of rabbits, Am. J Physiol. 179:599 1954.

16. Masson, G. M C., Corcoran, A. C. nd Page, I H Some effects of chronic treatment of ats with renin, Am J Physiol 162:379 1950.

17 Masson, G. M C Kashu, Ch., M tsunaga, M. nd Page I H Hypertensive vascular disease produced by homologous renin, Science 145 178, 1964

Some effects of diphenylhydantoin and propranolol on the cardiovascular system

Winifred G. Nayler, D.Sc.
I. McInnes, F.R.C.S., F.R.A.C.S.
J. B. Swann, M.B., B.S.
D. Race, M.B., B.S.
Valerie Carson, M.Sc.
T. E. Lowe, D.Sc., M.D., F.R.C.P., F.R.A.C.P.
Melbourne, Australia

Diphenylhydantoin sodium (Dilantin), which is used clinically for the treatment of epilepsy, was shown by Finkelman and Arieff[1] to evoke electrocardiographic ST and T wave changes. More recently Bernstein and associates[2] and Conn[3] have advocated its use in the treatment of certain cardiac arrhythmias, including those which proved to be refractory to the conventional modes of antiarrhythmic therapy. Bernstein and associates[2] postulated that the antiarrhythmic action of diphenylhydantoin may reflect a direct effect of the drug on the permeability of cardiac muscle cells to ionized sodium and potassium. Little information is available about the general effect of diphenylhydantoin on the cardiovascular system. The following experiments were designed to determine its effect on the peripheral circulation and on the work capacity of the left ventricle, and then to compare these effects with those induced by the similar administration of the recently introduced antiarrhythmic beta-adrenergic antagonist propranolol.[4]

Methods

Anesthesia. Healthy mongrel dogs (15 to 20 kilograms) were premedicated with 30 mg. morphine sulphate intramuscularly approximately one hour before anesthesia was induced with sodium thiopentone (20 to 30 mg. per kilogram intravenously). A surgical level of anesthesia was maintained throughout the experiment by giving small supplementary doses of thiopentone from time to time as required. Ventilation was maintained with oxygen from a positive pressure respirator through a cuffed endotracheal tube at a rate of 2 liters per minute.

Part I. Effect of diphenylhydantoin sodium (Dilantin) on the peripheral circulation. Dogs on heart-lung bypass perfused under conditions of (a) constant flow or (b) constant perfusion pressure were used to investigate the effect of diphenylhydantoin on regional blood flow. The method used for studying regional blood flow has been described in detail previously.[5]

Dogs were placed on heart-lung bypass using a Kay Cross disk oxygenator primed

From Baker Medical Research Institute, Victoria, Australia.
This investigation was carried out during the tenure of a grant-in-aid from the National Heart Foundation of Australia.
Received for publication Feb. 20, 1967.
Address: Baker Medical Research Institute, Commercial Road, Prahran, S.1., Victoria, Australia.

with homologous blood and 5 per cent dextrose (3:1). The oxygenator was gassed with 100 per cent O_2 and the temperature of the perfusing blood was maintained at 37°C. by means of a stainless steel heat exchanger in the arterial inflow line. The vascular system was perfused by means of a nonpulsatile (Mono Pumps, Pty. Ltd. Australasia) pump through the right carotid artery at flow rates of or in excess of 100 ml. per kilogram per minute. Appropriate cannulation allowed the independent measurement of venous outflow from the splanchnic renal lower inferior vena cava (IVC) superior vena cava (SVC) and vena azygos vascular fields and coronary sinus. Blood flow through a particular field was measured before and after diphenylhydantoin was added by clamping the connection between the particular graduated cylinder and the reservoir and measuring the time required to collect 100 ml. of blood. Preliminary experiments showed that pressure in the cannulated venous segments did not change during the collection procedure. Changes in flow due to an opposing pressure head developing during timed collection of blood in the measuring cylinders therefore were negligible for the purposes of these experiments. Samples of arterial and coronary sinus blood were taken as required to estimate the percentage oxyhaemoglobin saturation which was determined spectrophometrically by a modification of the method of Roos and Rich.[4]

In three heart lung bypass preparations perfused under conditions of constant pressure the effect of diphenylhydantoin on the coronary circulation was determined after ventricular fibrillation had been induced by applying 10 volts DC between two points on the anterior surface of the heart. In another four preparations diphenylhydantoin was added after beta adrenergic blockade had been established with 1 mg. per kilogram of propranolol.

Part 2. Effect of diphenylhydantoin sodium (Dilantin) and propranolol on left ventricular work function. Left ventricular work function curves were constructed from a series of experiments before and during the sixty minutes which followed intravenous administration of either diphenylhydantoin or propranolol using a modification of the method originally described by Stirling Morris and Race.

Left ventricular work function at a particular flow was calculated from the formula

$$W = Q \times (P_{A_0} - P_{L_A})$$

where

W = left ventricular work (Gm. cm./min.),
Q = flow (ml./min.)
P_{A_0} = cm. H_2O pressure in femoral artery and
P_{L_A} = cm. H_2O pressure in left atria.

The term work is used in accordance with its common cardiologic usage in the context of Frank Starling work study curves. Strictly speaking the parameters used are those of power i.e. work per unit time.

The experimental preparation used is shown schematically in Fig. 1.

Through a sternal splitting thoracotomy the heart and great vessels were exposed and the pericardium opened. Cannulae were inserted into the superior vena cava (SVC) through the proximal stump of the ligated vena azygos and into the inferior vena cava (IVC) through the right atrial appendage. Tapes were passed around the SVC, IVC and the pulmonary artery and an inflow cannula was placed through the wall of the right ventricle and positioned so that its tip lay in the main pulmonary artery distal to the tape. In this way venous return from the great veins was diverted by gravity drainage to a venous reservoir and thence returned by a nonpulsatile pump (Mono Pumps, Pty. Ltd. Australasia) into the pulmonary artery. The inflow to the heart and hence cardiac output could be controlled therefore by adjusting the output of the pump. A cannula was inserted through the wall of the right ventricle to drain the total coronary sinus and Thebesian vein return which was then diverted to a graduated cylinder and then to the venous reservoir. Coronary blood flow was measured by clamping the connection between the graduated cylinder and the reservoir and measuring the time required to collect 100 ml. blood. The clamp was then released and the blood allowed to return to the venous reservoir. After all dissection was

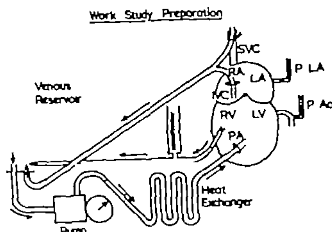


Fig 1 Schematic representation of experimental circuit used for left ventricular function studies. *P LA* refers to pressure in left atrium and *P AO* to systemic arterial pressure measured in the femoral artery

completed and prior to inserting the cannulas, the dogs were heparinized (2 mg per kilogram per hour)

Left atrial pressure was measured with a saline manometer connected to a cannula inserted into the left atrium through a branch of the inferior pulmonary vein. Mean systemic pressure was measured with a damped mercury manometer connected to a catheter placed in the left femoral artery

In a series of preparations the output of the pump and hence inflow to the left atrium was varied from 60 to 160 ml. per kilogram per minute in increments of approximately 10 ml per kilogram per minute before and after the addition of either diphenylhydantoin or propranolol. As soon as stable conditions were re-established after each increase in flow mean systemic arterial and mean left atrial pressures were recorded and calculated and left ventricular work plotted against left atrial pressure.

Part 3 Effect of diphenylhydantoin sodium (Dilantin) and propranolol on myocardial contractions The direct effect of diphenylhydantoin on cardiac contractions was determined using small papillary muscles excised from freshly exsanguinated dogs. Isolated papillary muscles were suspended isometrically in aerated (95 per cent O_2 + 5 per cent CO_2) Tyrode's solution maintained at 37°C and which had the following composition (mM) NaCl 130 KCl 5 6 $CaCl_2$ 1 6 $NaHCO_3$ 25 0 sucrose, 12 1 glucose 11 1 NaH_2PO_4 9 1 $MgSO_4$ 1 14 It was prepared from Merck Analytical Reagent grade chemicals dissolved in all-glass distilled water. Isometric conditions were maintained by applying 5 Gm. tension. Stimulation was effected with suprathreshold rectangular pulses of 10 msec duration from a Tektronix pulse generator at a rate of 55 pulses per minute. Contractions were detected with micro sensor semiconductor strain gauges (type MSE 132 120) arranged to form a wheatstone bridge, the output of this bridge being displayed on an ultraviolet light photographic recorder (S.E. Laboratories, type 200 S). Each preparation was equilibrated in Tyrode's solution for 60 minutes prior to the addition of drugs.

Drugs The following drugs were used sodium thiopentone (as Pentothal May & Baker Ltd Australia) propranolol (as Inderal I C I 45,520 Imperial Chemical Industries, England) isoproterenol (as Isuprel Winthrop Laboratories, Australia) d phenylhydantoin sodium (as Dilantin Parke Davis & Company Michigan) angiotensin (as Hypertensin Ciba Basel)

Results

Part 1 Effect of diphenylhydantoin sodium (Dilantin) on the peripheral circulation Preliminary studies indicated that the regional distribution of blood in dog heart lung preparations remained rela-

*Table I Effect of 3.5 mg/Kg of diphenylhydantoin sodium (Dilantin) on regional blood flow**

	Mean systemic blood pressure	Coronary	Renal	I V C	S V C	Splanchnic	Vena azygos
Regional blood flow (ml./min./Kg.)							
Control	88 ± 3 6	10 6 ± 1 1	14 6 ± 3 1	26 5 ± 2 1	43 8 ± 5 1	51 4 ± 1 1	18 4 ± 1 0
Dilantin	78 ± 3 7	10 6 ± 1 1	13 4 ± 3 2	29 0 ± 2 2	44 0 ± 5 1	49 0 ± 1 3	18 3 ± 1 4
Regional blood flow (% total flow)							
Control		6 3 ± 0 4	9 3 ± 2 5	15 9 ± 0 6	26 0 ± 2 4	31 3 ± 0 9	11 1 ± 0 4
Dilantin		6 4 ± 0 5	8 6 ± 2 5	17 5 ± 0 6	26 2 ± 2 2	29 9 ± 1 0	11 3 ± 0 3

*Mean ± standard error Five constant pressure preparations.

*Table II Effect of 3.5 mg/Kg diphenylhydantoin sodium (Dilantin) on regional blood flow**

	Mean blood pressure (mm Hg)	Coronary	Renal	I V C	S V C	Splanchnic	Vena azygos
Regional blood flow (ml/min./Kg)							
Control	76 ± 0 5	5 8 ± 0 3	16 7 ± 3 3	17 3 ± 0 9	18 8 ± 2 6	39 3 ± 3 6	12 1 ± 0 2
Dilantin	76 ± 0 5	11 5 ± 1 7	12 6 ± 2 2	26 2 ± 1 4	28 0 ± 6 5	37 3 ± 3 5	16 5 ± 1 2
Regional blood flow (% total flow)							
Control		5 4 ± 0 4	14 8 ± 3 1	15 2 ± 1 7	17 0 ± 2 1	35 5 ± 1 9	10 5 ± 0 6
Dilantin		8 4 ± 0 6	9 7 ± 1 8	20 0 ± 2 5	19 5 ± 2 7	30 7 ± 2 0	11 7 ± 0 4

*Mean ± standard error Four constant pressure preparations.

tively constant during three hours bypass.

CONSTANT TOTAL FLOW CONDITIONS The addition of 3.5 mg per kilogram of diphenylhydantoin to dog heart lung bypass preparations perfused under conditions of constant total flow immediately resulted in a small fall in mean systemic pressure and a changed distribution of blood in the peripheral circulation The results from 5 preparations, summarized in Table I show that the diphenylhydantoin-induced fall in systemic pressure was accompanied by a small but consistent increase in the percentage of total blood flow which passed through the IVC (hind limb and pelvis) circulation. The proportion of blood which flowed through the coronary SVC and vena azygos fields was essentially unchanged despite the slight fall in systemic pressure

Comparable changes in the regional distribution of blood occurred when diphenyl

Table III Effect of 3.5 mg/Kg of diphenylhydantoin sodium (Dilantin) on myocardial oxygen consumption

Experiment	Preparation No.	Systemic pressure (mm Hg)	Coronary flow (ml/min.)	Coronary A-V O_2 difference (% saturation)	Oxygen consumption index Coronary flow times A-V O difference
A. *Constant perfusion pressure*					
B	24	85	89 5	42 2	3 768
A		85	210	17 8	3 738
A		85	214	17 3	3 702
B	25	80	120	29 3	3 516
A		80	175	19 5	3 413
A_{15}		80	158	19 4	3 065
B	26	90	100	33 6	3 360
A		90	143	21 5	3 074
A		90	158	19 4	3 065
B *Constant total flow*					
B	9	95	110	31 3	3 443
A_4		85	106	32 0	3 392
A		85	106	32 0	3 392

*Where B, A_5 and A_{15} are readings taken before and then 5 and 5 minutes after 3 5 mg per kilogram of diphenylhydantoin was added.

hydantoin was added to 4 other dog heart lung bypass preparations 20 minutes after 1 mg per kilogram of propranolol had been added The effectiveness of the propranolol-induced beta-adrenergic blockade was established for each of these preparations by observing the failure of 1 0 μg per kilogram of intravenous isoproterenol to cause any fall in systemic pressure or increase in heart rate.

The fall in systemic pressure which followed the addition of diphenylhydantoin persisted for approximately 25 minutes. The addition of 1 μg per kilogram of angiotensin during the diphenylhydantoin-induced period of reduced systemic pressure resulted in a pressor response which did not differ in magnitude from that which followed an initial addition of angiotensin before diphenylhydantoin was added.

CONDITIONS OF CONSTANT PERFUSION PRESSURE. When 3.5 mg per kilogram of diphenylhydantoin was added to dog heart lung bypass preparations perfused under conditions of constant perfusion pressure the changed regional distribution of blood became more marked. The results from 4 preparations are summarized in Table II and indicate that 3 5 mg per kilogram diphenylhydantoin caused a reduction in the resistance to blood flow in the coronary and IVC circulations and to a lesser extent, in the vena azygos and SVC circulation The resistance to blood flow in the splanchnic and renal circulations, however increased. These changes were not modified by prior beta-adrenergic blockade with 1 mg per kilogram propranolol Diphenylhydantoin similarly reduced the resistance to blood flow in the coronary circulation of those heart-lung bypass preparations in which ventricular fibrillation had previously been established

Effect of diphenylhydantoin sodium (Dilantin) on myocardial oxygen consumption The diphenylhydantoin induced reduction in the resistance to blood flow in the coronary circulation of dogs on heart lung bypass was associated with a small decline in the rate at which the myocardium used oxygen The results from four typical preparations are listed in Table III

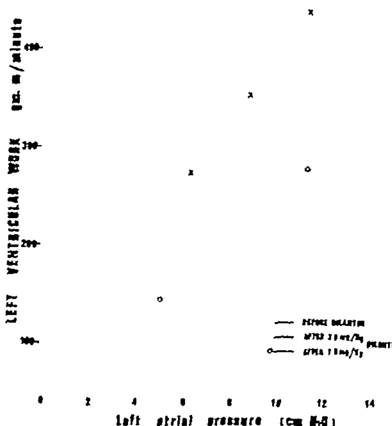


Fig. 2. Left ventricular work function curves recorded from a typical preparation (No. 33) before and after the addition of 3.5 or 7.0 mg. per kilogram of diphenylhydantoin, as indicated. Note that 3.5 mg. per kilogram of diphenylhydantoin failed to change the work function curve. 7.0 mg. per kilogram of diphenylhydantoin caused the curve to be flattened and displaced to the right.

Part 2. Effect of diphenylhydantoin sodium (Dilantin) and propranolol on ventricular function

LEFT VENTRICULAR WORK FUNCTION STUDIES

Dilantin. In an initial series of control experiments the inflow to the left atrium was varied from 60 to 160 ml. per kilogram per minute by varying the output of the pump in increments of 10 ml. per kilogram per minute. As soon as stable conditions were re-established after each particular increase in flow mean systemic arterial and left atrial pressures were recorded. Calculated left ventricular work when plotted against left atrial pressure yielded a curve which had a steep slope indicating, as is shown by the control curve for Fig. 2, that large increments in left ventricular work resulted from only small increments in left atrial pressure. Preliminary studies showed that left ventricular work function curves were reproducible for each particular preparation.

After 3.5 mg. per kilogram of diphenylhydantoin had been added the left ventricular work function curve for any one preparation was not markedly different from that recorded from the same preparation before the addition of diphenylhydantoin. The left ventricular work function curves recorded from a typical preparation before and after the addition of diphenylhydantoin are displayed in Fig. 2 and the results from 5 other preparations are listed in Table IV.

When 7 mg. per kilogram of diphenylhydantoin was added the left ventricular

Table IV Effect of diphenylhydantoin sodium (Dilantin) on relationship between left ventricular "work" and left atrial pressure

Preparation No.	Experiment	Left ventricular "work" (Gm. M./min.)				
		Left atrial pressure (cm. H_2O)				
		2	4	6	8	10
6	Before	135	160	275	350	450
	After 3.5 mg./Kg. Dilantin	135	155	280	360	400
7	Before	120	170	290	380	420
	After 3.5 mg./Kg. Dilantin	120	170	285	360	420
8	Before	105	146	220	276	300
	After 3.5 mg./Kg. Dilantin	110	140	215	270	310
17	Before	155	330	410	505	575
	After 3.5 mg./Kg. Dilantin	145	326	400	510	570
18	Before	105	180	265	330	460
	After 3.5 mg./Kg. Dilantin	100	175	260	350	455
19	Before	120	160	240	295	350
	After 7.0 mg./Kg. Dilantin	95	130	160	210	220
20	Before	100	140	220	270	320
	After 7.0 mg./Kg. Dilantin	78	120	158	190	220
21	Before	100	160	275	340	380
	After 7.0 mg./Kg. Dilantin	65	110	130	220	240

Table V Effect of diphenylhydantoin sodium (Dilantin) on relationship between left ventricular "work" and coronary blood flow

Preparation No.	Experiment	Coronary blood flow (ml./min.)				
		Left ventricular "work" (Gm. M./min.)				
		100	200	300	400	500
6	Before	75	78	83	92	104
	After 3.5 mg./Kg. Dilantin	76	80	85	92	105
7	Before	92	95	98	105	115
	After 3.5 mg./Kg. Dilantin	90	95	100	108	118
8	Before	60	65	72	80	95
	After 3.5 mg./Kg. Dilantin	60	68	75	82	100
17	Before	80	92	105	115	125
	After 3.5 mg./Kg. Dilantin	78	94	108	115	130
18	Before	75	88	110	135	146
	After 3.5 mg./Kg. Dila tin	75	88	115	140	150
19	Before	70	82	90	105	126
	After 7.0 mg./Kg. Dilantin	110	125	136	—	—
20	Before	62	70	82	96	108
	After 7.0 mg./Kg. Dilantin	98	116	126	—	—
21	Before	62	65	78	84	95
	After 7.0 mg./Kg. Dila tin	84	110	136	—	—

work function curves were consistently displaced to the right and flattened compared with that of the control preparation. Such a curve is included in the data shown in Fig. 2. The results from 3 other preparations are included in Table IV. This change in myocardial function occurred immediately after the higher concentration of diphenylhydantoin was added and persisted for approximately sixty minutes.

The addition of 3.5 mg. per kilogram of diphenylhydantoin to these preparations failed to cause any significant change in the ratio between calculated left ventricular work and coronary blood flow, as is shown by the data displayed in Fig. 3 and other data summarized in Table V. Additional data shown in Fig. 3 and Table V show that when 7.0 mg. per kilogram of diphenylhydantoin was added, coronary flow increased at each particular level of calculated left ventricular work relative to that of the control preparation.

Propranolol. The addition of 0.5 mg. per kilogram of propranolol resulted in the left ventricular work function curve being displaced to the right and flattened relative to that recorded from the same preparation during the control period before propranolol was added. Left ventricular function curves recorded from a typical preparation before and after the addition of 0.5 mg. per kilogram of propranolol are shown in Fig. 4 and indicate that propranolol caused a decline in the capacity of the left ventricle to perform work even when the left atrial pressure was comparatively low. The results from four other preparations are listed in Table VI. Other data listed in Table VI indicate that the addition of 1.0 mg. per kilogram of propranolol to 4 other preparations similarly resulted in a decline in the capacity of the left ventricle to perform work. These preparations all showed signs of left ventricular failure indicated by raised left atrial pressures and reduced left ventricular work. The propranolol-induced decline in left ventricular work capacity was associated with a reduced coronary blood flow. When left

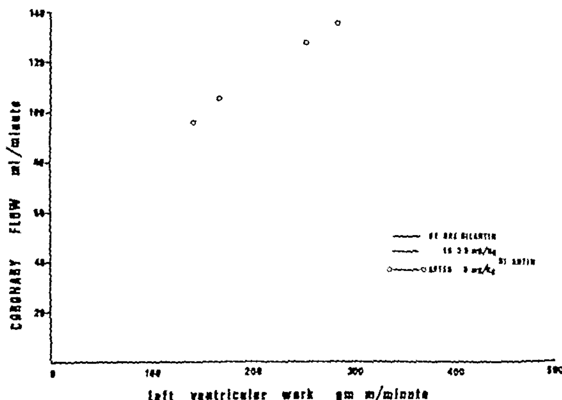


Fig. 3. Relationship between left ventricular work and coronary blood flow in typical preparation (N 33) before and after the addition of either 3.5 or 7.0 mg. per kilogram of diphenylhydantoin, as indicated.

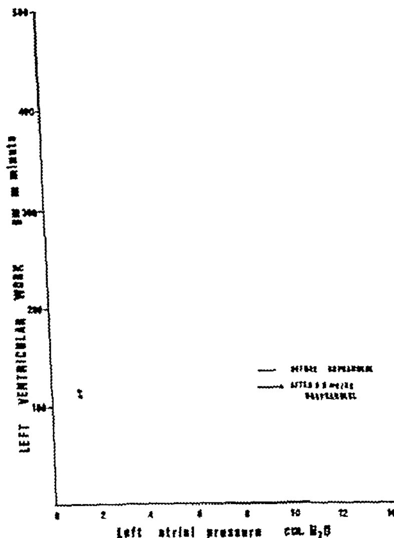


Fig 4 Left ventricular work function curves recorded from a typical preparation (N 40) before and after 0.5 mg per kilogram of propranolol as added, as indicated.

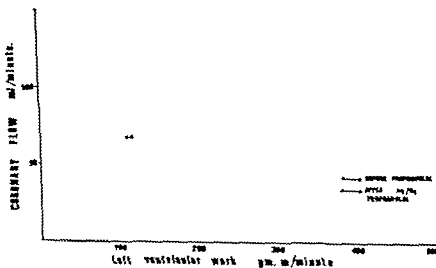


Fig 5 Relationship bet een left ventricular work and coronary blood flow in a typical preparation (N 40) befor and after 0.5 mg. per kilogram of propranolol was added as indicated.

Table VI. Effect of propranolol on relationship between left ventricular work and left atrial pressure

Preparation No.	Experiment	Left ventricular work (Gm. M./min.)				
		Left atrial pressure (cm. H_2O)				
		2	4	6	8	10
34	Before	126	270	370	415	450
	After 0.5 mg./Kg. propranolol	65	115	200	250	—
35	Before	70	90	300	475	600
	After 0.5 mg./Kg. propranolol	40	60	130	185	230
36	Before	110	300	420	515	610
	After 0.5 mg./Kg. propranolol	55	110	160	210	220
37	Before	160	350	430	320	380
	After 0.5 mg./Kg. propranolol	70	130	220	250	280
38	Before	120	275	390	475	540
	After 1.0 mg./Kg. propranolol	20	90	120	162	185
39	Before	100	260	415	515	600
	After 1.0 mg./Kg. propranolol	40	100	140	180	205
41	Before	80	210	310	395	470
	After 1.0 mg./Kg. propranolol	40	75	105	115	155
42	Before	—	—	90	280	435
	After 1.0 mg./Kg. propranolol	—	—	55	165	190

Table VII. Effect of propranolol on relationship between left ventricular work and coronary blood flow

Preparation No.	Experiment	Coronary blood flow (ml./min.)				
		Left ventricular work (Gm. M./min.)				
		100	200	300	400	500
34	Before	79	80	91	112	125
	After 0.5 mg./Kg. propranolol	55	55	68	—	—
35	Before	55	65	78	95	110
	After 0.5 mg./Kg. propranolol	35	50	55	—	—
36	Before	70	85	98	115	130
	After 0.5 mg./Kg. propranolol	45	52	55	—	—
37	Before	68	80	103	120	135
	After 0.5 mg./Kg. propranolol	62	55	57	—	—
38	Before	75	90	112	136	148
	After 1.0 mg./Kg. propranolol	58	62	65	65	—
39	Before	70	86	98	112	130
	After 1.0 mg./Kg. propranolol	57	58	59	59	—
41	Before	75	90	110	135	158
	After 1.0 mg./Kg. propranolol	55	58	60	60	—
42	Before	80	85	105	120	145
	After 1.0 mg./Kg. propranolol	62	60	—	—	—

Table VIII. Effect of diphenylhydantoin sodium (Dilantin) and of propranolol on tension produced by dog papillary muscle preparations during isometric contraction

Drug	Bath concentration (mg./L.)	No. of preparation	Stimulus rate (per min.)	% Change in tension $\left(\frac{B - A}{B} \times \frac{100}{1}\right)$
Dilantin	3 5	6	55	0
	7 0	6	55	−22 ± 4 0
Propranolol	0 1	8	55	−11 ± 2 5
	1 0	8	55	−22 ± 4 5
	2 0	8	55	−55 ± 2 0

*Where B refers to tension produced before and A after the addition of either Dilantin or propranolol as indicated. Mean results are shown.

ventricular work was plotted against coronary blood flow for preparations to which 0.5 to 1 0 mg. per kilogram of propranolol had been added the resultant curve was consistently flattened relative to that obtained from the same preparation before propranolol had been added. The results from a typical preparation are displayed in Fig. 5 and the results from another 8 preparations are summarized in Table VII. These results all show that after propranolol was added the coronary blood flow declined over a wide range of left ventricular work, relative to that recorded from the same preparation before propranolol was added.

Part 3. Effect of diphenylhydantoin sodium (Dilantin) and propranolol on myocardial contractions

DILANTIN. The tension produced during isometric contractions of isolated dog papillary muscles immersed in Tyrode's solution containing 3.5 mg. per liter diphenylhydantoin was not significantly different from that produced by the same preparation before diphenylhydantoin was added. The results from 6 such papillary muscle preparations are summarized in Table VIII. Other data listed in this same Table VIII show that after 7.5 mg. per liter diphenylhydantoin was added the tension produced during contraction decreased.

PROPRANOLOL. The addition of 0 1 mg. per liter propranolol to the Tyrode solution bathing freshly equilibrated papillary muscles resulted in a marked reduction in tension produced by these muscles during isometric contractions. This is shown by data listed in Table VIII. Other data listed in Table VIII show that the higher the concentration of propranolol the greater the decline in tension produced during contraction.

After being exposed to propranolol the continued immersion of these preparations in propranolol-free Tyrode's solution resulted in their contractions being restored to their pre-propranolol level.

Discussion

Since Harris and Kokernot reported in 1950 that the intravenous administration of diphenylhydantoin sodium (Dilantin) was effective in abolishing ventricular arrhythmias caused by coronary ligation repeated references have been made to the antiarrhythmic properties of this drug. Mosey and Tyler[1] found it to be effective in abolishing ouabain-induced ventricular tachycardia in dogs. Covino and associates[13] used it as an antiarrhythmic agent in hypothermic dogs. Sherf and associates used it to abolish aconitine and delphinine-induced atrial fibrillation and flutter and to control ventricular tachycardia and arrhythmias induced by the topical application of aconitine. In 1958 Leonard reported its effectiveness in the treatment of ventricular arrhythmias in a patient in whom other antiarrhythmic agents had been unsuccessful. More recently Conn described the results of a clinical survey in which he used 3.5 to 5 0 mg. of diphen

ylhydantoin per kilogram of body weight in patients presenting with cardiac arrhythmias and concluded that it was particularly effective in supraventricular and ventricular arrhythmias resulting from digitalis excess. It was also of benefit *in controlling atrial and ventricular arrhythmias.* Bernstein and associates[3] studied its effectiveness in 60 patients with recurrent cardiac arrhythmias resistant to conventional antiarrhythmic therapy (the arrhythmias including premature ventricular contraction paroxysmal atrial tachycardia paroxysmal atrial fibrillation premature atrial and premature nodal systoles, and chronic atrial flutter) and concluded that diphenylhydantoin is a useful addition to the armamentarium utilized in the treatment of recurrent cardiac arrhythmias. Although the antiarrhythmic properties of diphenylhydantoin are well documented little information is available about the effect on the circulation The results reported in this present study indicate that this drug causes an over all reduction in the *resistance to blood flow* in the peripheral circulation Since the resistance to blood flow in the coronary circulation was found to decline even in those preparations in which ventricular fibrillation *had deliberately* been induced the dilatory effect of diphenylhydantoin on the coronary circulation cannot be accounted for simply in terms of a change in the amount of external work being done by the *heart* Beta adrenergic blockade failed to modify the coronary vasodilator effect of diphenylhydantoin so that its action cannot be due simply to activation of beta adrenergic receptors in the coronary vasculature[13] Gupta and associates[14] have suggested that this dilator effect of diphenylhydantoin on the coronary circulation may be related to its antiarrhythmic properties.

The resistance to blood flow in the SVC and IVC circulations was decreased by diphenylhydantoin even when beta adrenergically blocked preparations were used. The resistance to blood flow in splanchnic and renal circulations, however increased slightly reflecting vasoconstriction in these particular vascular fields.

In the present study the effect of diphenylhydantoin on myocardial performance was investigated over a dynamic range of work and in the isometric studies at a particular level of work output Sarnoff and Berglund[7] have already shown that for any given circulatory state there *is a consistent relationship* between atrial pressure and ventricular stroke work and that displacement of ventricular work function curves to the left such as that which occurs after the infusion of catecholamines indicates an increased capacity for doing external work at the same atrial pressure, and hence at the same left ventricular end diastolic fiber length The results of the present study show that 3.5 mg per kilogram of diphenylhydantoin failed to displace the left ventricular work function curves, indicating that the capacity of the left ventricle to perform external work had not been modified The results of the isometric studies confirmed this finding Higher concentrations of diphenylhydantoin however displaced the work function curves to the right reflecting a *decline in left ventricular work capacity* This change in left ventricular work function was, in contrast with that caused by propranolol associated with an augmented coronary blood flow reflecting *the diphenylhydantoin induced reduction* in resistance to blood flow in this particular vascular field

The introduction of beta adrenergic antagonists for the control of cardiac arrhythmias[7,22] centered around the recognized influence of catecholamines on the mechanical and electrical properties of heart muscle Recent evidence suggests that the antiarrhythmic properties of these drugs[illegible] may actually be separate from their ability to produce beta adrenergic blockade. Their efficiency as antiarrhythmic agents is still disputed Recently Bacon and associates[illegible] reported that propranolol failed to reduce the incidence of arrhythmias and death rates in a clinical trial involving 114 patients, a finding which was confirmed in another recent trial series by Clausen and associates.[illegible]

Previous studies from these laboratories showed that propranolol increased the resistance to blood flow in the peripheral circulation of dogs on heart lung bypass,

and that it depressed myocardial contractions and coronary blood flow. McKenna and associates[32] investigated the systemic and coronary hemodynamic effects of propranolol in dogs and recorded a decrease in cardiac output and ventricular work accompanied by an increased peripheral pulmonary and coronary vascular resistance. Earlier Epstein and associates[33] reported that the administration of propranolol to normal subjects during submaximal exertion resulted in a decline in cardiac output, heart rate, mean arterial pressure and left ventricular minute work. The present results show that propranolol displaces left ventricular work function curves to the right and therefore indicate that propranolol-induced beta adrenergic blockade results in a decline in the capacity of the left ventricle to perform external work at a particular end diastolic fiber length. These results resemble those of Arbulu and Thal[32] who used pronethalol to induce beta adrenergic blockade.

The propranolol induced decline in the capacity of the left ventricle to perform external work differed from that which followed the administration of high concentrations of diphenylhydantoin in that it was associated with a decreased coronary blood flow. This propranolol induced decline in coronary blood flow may reflect the unmasking during beta blockade of the effect of endogenous catecholamines on the alpha-receptors in the coronary circulation.[34-4]

Summary

The effect of diphenylhydantoin sodium (Dilantin) on the peripheral circulation and on the work capacity of the left ventricle was studied and compared with that of another antiarrhythmic drug, the beta adrenergic antagonist propranolol.

Dilantin (3.5 mg. per kilogram) caused a decline in the resistance to blood flow in the peripheral circulation and in particular in the coronary, IVC and SVC circulations. This action of Dilantin was not mediated through the beta-adrenergic receptors.

Dilantin (3.5 mg. per kilogram) failed to modify left ventricular work function curves; higher concentrations of diphenylhydantoin did, however, depress the capacity of the left ventricle for performing external work. This Dilantin induced decline in left ventricular work capacity contrasts with that caused by propranolol in that it was associated with an augmented coronary blood flow over a wide range of left ventricular work.

Supplies of propranolol were generously donated by the Imperial Chemical Industries, England.

REFERENCES

1. Finkelman, I., and Arieff, A. J.: Untoward effects of phenytoin sodium in epilepsy, J. A. M. A. 118:1209, 1942.
2. Bernstein, H., Gold, H., Tao-Wang Lang, Pappelbaum, S., Bazika, V., and Corday, E.: Sodium diphenylhydantoin in the treatment of recurrent cardiac arrhythmias, J. A. M. A. 191:695, 1965.
3. Conn, R. D.: Diphenylhydantoin sodium in cardiac arrhythmias, New England J. Med. 272:277, 1965.
4. Ahlquist, R. P.: A study of the adrenotropic receptors, Am. J. Physiol. 153:586, 1948.
5. Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H., and Dornhorst, A. C.: A new adrenergic beta-receptor antagonist, Lancet 1:1080, 1964.
6. Nayler, W. G., McInnes, I., Swann, J. B., Carson, Valerie, and Lowe, T. E.: Effect of propranolol, a beta-adrenergic antagonist, on blood flow in the coronary and other vascular fields, Am. Heart J. 73:207, 1967.
7. Nayler, W. G., Race, D., Price, J. M., and Lowe, T. E.: Some effects of a cardio-active fraction isolated from human blood plasma on the peripheral circulation, Circulation Res. 18:1, 1966.
8. Roos, A., and Rich, J. A.: Spectrophotometric determination of oxyhaemoglobin saturation and oxygen content of blood, J. Lab. & Clin. Med. 40:431, 1952.
9. Sterling, G. R., Morris, K. N., and Race, D.: The effect of induced asystole on ventricular function, Australian New Zealand J. Surg. 31:81, 1961.
10. Harris, A. S., and Kokernot, R. H.: Effects of diphenylhydantoin sodium (Dilantin sodium) and phenobarbital sodium upon ectopic ventricular tachycardia in acute myocardial infarction, Am. J. Physiol. 163:505, 1950.
11. Mosey, L., and Tyler, M. D.: Effect of diphenylhydantoin sodium (Dilantin), procaine hydrochloride, procaine amide hydrochloride and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65, 1954.
12. Covino, B. G., Wright, R., and Charleson, D. A.: Effectiveness of several antifibrillatory drugs in the hypothermic dog, Am. J. Physiol. 181:54, 1955.
13. Scherf, D., Blumenfeld, S., Taner, D., and

Yildiz, M. The effect of diphenylhydantoin (Dilantin) sodium on atrial flutter and fibrillation provoked by focal application of aconitine or delphinine, Am. Heart J. 60:936, 1960.

14. Leonard, W. A., Jr. Use of diphenylhydantoin (Dilantin) sodium in treatment of ventricular tachycardia, Arch. Int. Med. 101:714, 1958.

15. Klocke, F. J., Kaiser, G. A., Ross, J., and Braunwald, E. An intrinsic adrenergic vasodilator mechanism in the coronary vascular bed of the dog, Circulation Res. 16:376, 1965.

16. Gupta, D. N., Metin, M. O., Basbour, F. A., and Webb, W. R. Effects of diphenylhydantoin (Dilantin) on coronary and systemic circulation, Clin. Res. 14:81, 1966.

17. Sarnoff, S. F., and Bergland, E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation 4:707, 1954.

18. Black, J. W., and Stephenson, J. S. Pharmacology of a new adrenergic beta-receptor blocking compound (nethalide), Lancet 2:311, 1962.

19. Sekiya, A., and Vaughan, Williams, E. M. A comparison of the antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide and quinidine, Brit. J. Pharmacol. 21:473, 1963.

20. Stock, J. P. P., and Dale, N. Beta-adrenergic receptor blockade in cardiac arrhythmias, Brit. M. J. 2:1230, 1963.

21. Besterman, E. M. M., and Friedlander, D. H. Clinical experiences with propranolol, Post grad. M. J. 41:526, 1965.

22. Snow, P. J. D. Effect of propranolol in myocardial infarction, Lancet 2:551, 1965.

23. Taylor, R. R., and Halliday, E. J. Beta adrenergic blockade in the treatment of exercise-induced paroxysmal ventricular tachycardia, Circulation 32:778, 1965.

24. Benfey, B. G., and Varma, D. R. Antisympathomimetic and antifibrillatory effects of pronethalol and propranolol, Brit. J. Pharmacol. 26:3, 1966.

25. Lucchesi, B. R. The effects of pronethalol and its dextro isomer upon experimental cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 148:94, 1965.

26. Nayler, Winifred G. The effect of pronethalol and propranolol on lipid-facilitated transport of calcium ions, J. Pharmacol. & Exper. Therap. 153:479, 1966.

27. Wolfson, S., Robbins, S. L., and Krasnow, N. Treatment of cardiac arrhythmias with beta-adrenergic blocking agents, Am. Heart J. 72:177, 1966.

28. Szekely, P., Jackson, F., Wynne, N. A., Vohra, J. K., Batson, G. A., and Dow, W. I. M. Clinical and experimental observations on the use of propranolol in disorders of cardiac rhythm, in Symposium on beta adrenergic receptor blockade, Am. J. Cardiol. 18:426, 1966.

29. Balcon, R., Jewitt, D. E., Davies, J. P. H., and Oram, S. A controlled trial of propranolol in acute myocardial infarction, Lancet 2:917, 1966.

30. Clausen, J., Felsby, M., Schønau Jørgensen, F., Lyager Nielsen, B., Roin, J., and Strange, B. Absence of prophylactic effects of propranolol in myocardial infarction, Lancet 2:920, 1966.

31. McKenna, D. H., Corliss, R. J., Sialer, S., Zarnstorff, W. C., Crumpton, C. W., and Rowe, G. G. Effect of propranolol on systemic and coronary hemodynamics at rest and during simulated exercise, Circulation Res. 19:520, 1966.

32. Epstein, S. E., Robinson, B. F., Kahler, R. L., and Braunwald, E. Effects of beta adrenergic blockade on the cardiac response to maximal and submaximal exercise in man, J. Clin. Invest. 44:1745, 1965.

33. Arbulu, A., and Thal, A. P. The hemodynamic effect of alpha and beta adrenergic blockade, Surgery 60:60, 1966.

34. Shapur, Naimi, and Proger, Samuel. Propranolol in myocardial infarction, Lancet 2:1465, 1966.

35. Harris, W. S., Schoenfeld, C. D., Brooks, R. H., and Weissler, A. H. Effect of beta adrenergic blockade on the hemodynamic response to epinephrine in man, Am. J. Cardiol. 17:484, 1966.

Case reports

Intermittent normalization of the right ventricular hypertrophy pattern in tetralogy of Fallot

Alexander Neuman M.D
Joseph H Yahini M.D F.A C C
Henry N Neufeld M.D F.A C C
Haifa Israel

Right ventricular hypertrophy of the adaptation type is the usual electrocardiographic pattern in cyanotic tetralogy of Fallot A few exceptional cases with the Wolff Parkinson Wh te syndrome[1,2] or with the electrocardiographic pattern observed in pulmonic stenosis with normal aortic root, or with left axis deviation and counterclockwise rotation of the frontal vectors have been reported Four unusual cases with normal electrocardiograms are mentioned in the literature, but only one of them has been documented

To the best of our knowledge this is the first reported case of tetralogy of Fallot displaying intermittently a normal electrocardiogram alternating in the same tracing with right ventricular hypertrophy pattern Besides its rarity this combination presents a challenge regarding the explanation of the observed electrocardiographic features.

Case report

D B was fou years of age hen she first came under our care in 1955 The presumptive diagnosis was cyanotic tetralogy of F llot without dextrocardia. This diagnosis was substantiated by right heart catheterization in January 1963 The findings t that time were The catheter entered directly from the right entricle into the ascending aorta right ventricular pressure was 120/5 mm. Hg main pulmonary artery pressure was 15/5 mm. Hg aortic pressure 115/70 mm. Hg and oxygen saturation in the aorta was 76 per cent A persistent left superior vena cava emptying into the coronary sinus was revealed as an additional anomaly The diagnosis of severe tetralogy of F llot was confirmed during corrective surgery which was performed on March 3 1964. According to the surgeon operative report high and large entricular septal defect between the septum and the anterior wall were present. There was tightly stenotic bicuspid pulmonary valv and severe infundibular stenosis ith markedly hypertrophied right ventricle. The presence of persistent left superior vena cava was confirmed, and an anomaly of the coronary arteries (lack of the descending branch of the left coronary artery), which was not suspected preoperatively was detected.

The most unusual finding in this case concerned the electrocardiogram which on different occasions, showed two distinctly different patterns. One of them (Fig 1) displayed the presence of right ven tricular hypertrophy with the mean spatial QRS vector poi ting anteriorly and to the right with normal QRS duration (0.07 to 0.08 second) This pattern was consistently accompanied by short PR (0 10 t 0 11 second) and PJ (0 17 to 0.19 second) intervals and by bizarre P waves, negativ in V_4, and suggestive of dome and dart configuration in V The second pattern (Fig 2) was normal and most unusual for tetralogy of Fallot or for such degree of anatomically proven right ventricular hypertrophy and systemic right ventricular pressure. The QRS complexes were 0.06 to 0.07 second in duration, there were S complexes in the right

From The Central Clinic of the Labour Sick Fund, Haifa, Israel (Dr Neuman), and the Heart Institute, Tel-Hashomer Government Hospital, The University of Tel-Aviv Medical School (Drs Yahini and Neufeld).
Received for publication Feb. 24, 1967

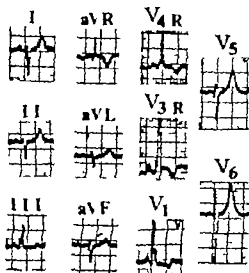


Fig. 2 Electrocardiograms showing right ventricular hypertrophy pattern with short PR and PJ intervals, positive P waves in right precordial leads and negative P waves in left precordial leads. Note the first P lead V suggestive of dome and dart configuration (see text).

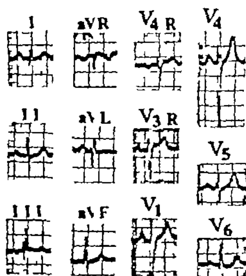


Fig. Electrocardiograms recorded on another occasion showing normal QRS pattern with longer PR and PJ intervals and normal shape and polarity of P waves (see text

precordial leads and qR complexes in V the PR and PJ intervals were 0.16 to 0.17 second and 0.22 to 0.24 second respectively with P waves of normal shape and polarity

On several occasions it was possible in most leads to record the transitional stages between the two patterns, with intermediate PR and PJ intervals and intermediate P waves and QRS complexes (*Fig. 3*).

Discussion

In a case of tetralogy of Fallot it would seem natural for the first of the two patterns to be the expression of right ventricular hypertrophy. On the other hand it is difficult to imagine an electrocardiographic pattern produced by *right ventricular hypertrophy* that could appear and disappear intermittently.

The only conceivable explanation for *transient normalization* of such a pattern would be that the right ventricular vectors are transiently balanced by oppositely directed electromotive forces. This could come about only by a ventricular parasystole competing with the sinus rhythm. This possibility can be dismissed in this case: apart from the unaccountable P wave changes, one would not expect the right ventricular hypertrophy pattern to be balanced by the ectopic beats after the *longer PR intervals*.

If the right ventricular hypertrophy pattern in this case is not the direct expression of ventricular hypertrophy then it must be explained in terms of impulse formation and/or conduction disturbances.

Congenital abnormalities of the conduction system have been shown to exist in congenital heart disease and to account for abnormal electrocardiographic patterns.[3,4] An abnormal course and morphology *of the right bundle branch* has been found in several congenital lesions, including tetralogy of Fallot and has been thought to result in early left bundle branch system activation.

The following possibilities may be considered in our case.

1 Influence of the autonomic system. Supraventricular impulse formation and conduction are under the control of this system. However the autonomic nervous system is not usually considered a factor directly influencing the intraventricular conduction. Therefore while vagal sympathetic tone fluctuations can account for *the simultaneous P wave and PR interval* alteration they cannot explain the concommitant QRS changes. Intermittent right bundle branch block could explain the phasic QRS changes, but these would be expected to result from autonomic nervous system fluctuations only indirectly through a changing heart rate. Such de-

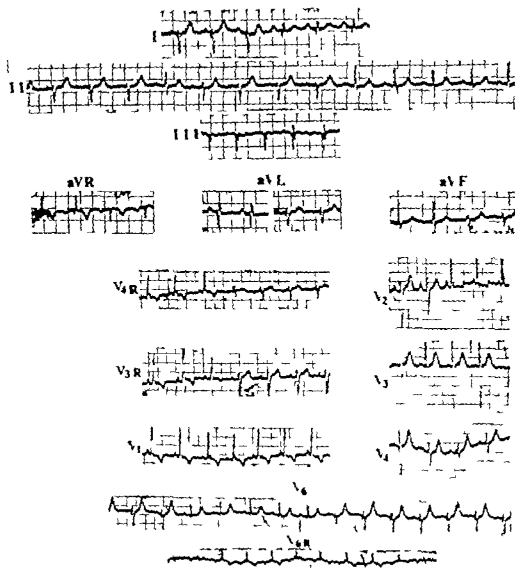


Fig. 3. Electrocardiogram showing the transition between the patterns seen in Figs. 1 and 2. Note intermediate P waves, PR intervals and QRS complexes (see text).

pendency on heart rate was not observed in our case in numerous tracings recorded on different occasions.

2. Bilateral bundle branch block. Longer PR-intervals with normal QRS complexes alternating with shorter PR intervals with abnormal QRS complexes may be due to a changing degree of incomplete bilateral bundle branch block.[7,8] Equal degree of incomplete bundle branch block in both bundles would result in longer PR intervals with normal QRS complexes. If the conduction improves intermittently on one side, the PR interval becomes shorter and the contralateral bundle branch block becomes apparent. This mechanism could explain the simultaneous changes of PR intervals, and the QRS complexes as well as the intermediate forms but not the concommitant P wave alterations.

3. Supraventricular impulse transmitted with aberrant intraventricular conduction outside the refractory phase and in the absence of intraventricular block. These are found in the Wolff-Parkinson-White syndrome and in so-called nodal beats. Since typical preexcitation complexes have been shown to occur both with changing P

waves and with nodal beats it is only a matter of definition whether our case is considered a form of the Wolff Parkinson-White syndrome or an instance of aberrantly conducted supraventricular beats. It should be stressed however that the electrocardiographic pattern in our case does not conform to the classical Wolff Parkinson White pattern described in the literature, especially as far as the markedly fluctuating PJ intervals and the QRS shape in left precordial beats are concerned

Anatomic investigations, experimental evidence and the clinical experience concerning reciprocal beating and aberrant intraventricular conduction of supraventricular impulses have lent strong support to the concepts of physiologic longitudinal dissociation conduction through preferential paths, or dual A V conduction system [3] Some form of split A V conduction seems to offer the best explanation for the simultaneous change of P waves, PR intervals, and QRS complexes in our case

The changing P wave shape in the absence of a positional factor may be due either to intra atrial conduction disturbance wandering pacemaker within the sinus node transient coronary sinus rhythm [7] or transient nodal rhythm In our case the presence of dome and dart P waves in V_1 (Fig 1) and of negative P waves in V are very suggestive of an atrial pacemaker shifting from the right to the left atrium [8]

It is conceivable that the changing atrial excitation wave front intermittently triggers one of the possible mechanisms of split A V conduction This in turn could change the temporal relationship of the excitation of the bundle branches or of the ventricles and could lead to an intermittent right bundle branch block pattern in a manner similar to the one referred to as a variety of bilateral bundle branch block. However the electrocardiographic pattern would differ from the latter in displaying concomitant P wave changes and a normal range of varying PR intervals. With earlier excitation of the left bundle a shortened PR and right bundle branch block pattern could be produced while with later excitation of this bundle the PR interval would be longer and the normal shape of the QRS complexes may thus be conceived as fusion beats between supraventricular impulses conducted by two morphologically or functionally differing pathways. Similar cases have been reported [29,31]

If the changing P waves are due to the ectopic supraventricular versus sinus rhythm competition, then intermediate P waves are fusion P waves as a result of dissociated atrial stimulation Likewise the varying QRS complexes represent ventricular fusion beats produced by the split, dissociated ventricular stimulation. It follows that our case suggests a type of longitudinal dissociation involving the active impulse formation and conduction system of the heart starting at the atrial level continuing in the atrioventricular conduction pathways and ending at the level of the ventricular muscle

Summary

A case proved severe cyanotic tetralogy of Fallot displaying an intermittent right ventricular hypertrophy pattern alternating with a normal QRS pattern in the electrocardiogram is presented Simultaneously changing P waves PR and PJ intervals were also present The intermittent character of the right ventricular hypertrophy pattern could be accounted for only by disturbances of impulse formation and/or conduction The changing direction of the atrial depolarization suggests either altered intra auricular conduction or a wandering supraventricular pacemaker possibly to the left atrium. The shifting atrial depolarization wave front could trigger some mechanism of longitudinally dissociated atrio-ventricular conduction and alter the temporal relationship of left and right ventricular depolarization

The question is raised whether conduction disturbances do not play a greater role in the production of ventricular hypertrophy pattern in various disease states than hitherto suspected

REFERENCES

1 Comberlati, L Due casi di sindrome di Wolff Parkinson White in cardiomyopathia congenita pervia, Cuore Circulation 39 169 1955
2. De Oliveira, J M Mendelsohn, D Nogueira, C and Zimmerman, H A. W P W syndrome

and tetralogy of F llot, Am. J Cardiol. 2 111 1958.
3. Neufeld, H. N T tus, J L., DuShane, J W Burchell, H. B and Edwards, J E. Isolated ventricular septal defect of the persistent common trio-ventricular canal type Circulation 23:685, 1961
4. Levine, J and Gubner R. Tetralogy of Fallot in an adult with normal electrocardiogram. *The Ht. Cent. B ll. of St. Francis Hospital,* 20:2 1965.
5. Lev M The architecture of the conduction system in congenital heart disease. (Part I) Arch. Path. 65:174 1958. Cited by Neuf ld, H N and associates.
6. Feldt, R. H., DuShane J W and Titus, J L. Morphology of the conduction system in ventricular septal defect and tetralogy of F llot Correlation with the electrocardiogram, 38th scientific session of the Am. Heart Assoc. Abstracts in Circulation, 32 suppl. No. II 84, 1965
7 Lepeshkin, E. The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Prog Cardiovas. Dis. 6:445, 1964
8. Katz, L. N and Pick, A. Clinical lectrocardiography Part I The arrhythmias, Philadelphia, 1956, Lea & Febiger Inc.
9 Scherf D and Cohen, J The A-V node and selected cardiac arrhythmias, New York, 1964 Grune & Str tton, Inc.
10. Wolff L. Syndrome of short PR interval with abnormal QRS omplexes and paroxysmal tachycardia (Wolff Parkinson-White syndrome) Circulation 10:282, 1954
11 Kent, A F S. The right lateral auriculoventricular junction of the heart, J Physiol 22:48, 1947
12 Pick, A. Aberrant ventricular conduction of escaped beats preferential and accessory path ways in the A V junction, Circulation 13 702 1956.
13 Bordman, J L., Rokita, L., Kennamer R., and Prinzmetal, M Studies on the mechanism of ventricular activity XIV Clinical and experimental studies of accelerated auriculo-ventricular conduction, Circulation Res. 11:69 1955.
14 Moe, G. K., Preston, J B and Burlington, H Physiologic evidence for a dual A-V transmission system, Circulation Res. 4:357 1956.
15. Mahaim, J Kent fibres and the A V paraspecific conduction through the upper connections of the bundle of His-Tawara, Am. Heart J 33:651 1947
16. James, T N Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology Am. Heart J 62 756, 1961
17 Zahn, A. Experimentelle U tersuchungen ueber die Reizbildung im Atrioventrikularknoten, Arch. Ges. Physiol. 151:247 1913.
18. Bix, H H The electrocardiographic pattern of initial stimulation in the left auricle, Sinai Hosp. J (Baltimore) 2:2, 1953 Cited by Mirowski and associates.[19]
19 Mirowski, M Neill, C A., and Taussig, H. B. Left trial ectopic rhythm in mirror image dextrocardia, and in normally placed mal formed hearts. Reported of twelve cases with dome and dart P waves, Circulation 27:864 1963.
20. Goodman, R. M and Pick, A. An unusual type of intermittent A-V dissociation in acute rheumatic myocardi tis, Am. Heart J 61:259 1961.
21 W l-h, T J Ventricular aberration of A V nodal escape beats Comments concerning the mechanism of aberration, Am J Cardiol 10:217 1962.

Reflux of oxygenated blood into the pulmonary artery in severe mitral regurgitation

Constantine J. Tatooles, M.D.
James H. Gault, M.D.
*Dean T. Mason, M.D.**
John Ross, Jr., M.D.
Bethesda, Md.

In 1906 MacCallum and McClure[1] first suggested that the elevated left atrial pressure observed in experimental mitral regurgitation might be transmitted retrograde into the pulmonary arterial vascular bed. Subsequently, this aspect of the hemodynamic picture of mitral valvular regurgitation received little attention, although in a few patients with severe regurgitation and marked augmentation of left atrial pressure, a pressure rise that corresponded temporally with the v wave of the left atrial pressure pulse was recorded in the main pulmonary artery.[2] In certain patients with mitral regurgitation it seems likely that the pressure in the left atrium even may exceed transiently that in the pulmonary artery, and therefore the possibility exists that reflux of oxygenated pulmonary venous blood into the pulmonary arteries might occur during such a reversal of the pressure gradient.

The present report describes a patient with acquired valvular heart disease in whom the oxygen saturation was higher in the pulmonary artery than in the right ventricle and in whom an abnormally elevated level of inhaled krypton 85 gas also was found in the pulmonary arteries. No abnormal communication between the greater and lesser circulations was demonstrated, but severe mitral regurgitation resulted in a peak left atrial v wave pressure that was greater than the pressure recorded simultaneously in the pulmonary artery. The increased level of oxygenation in the pulmonary artery was abolished by corrective surgical treatment of the mitral valvular lesion. Therefore, pulmonary venous blood may move retrograde into the pulmonary arterial bed in the presence of severe mitral regurgitation, leading to a previously undescribed cause for the passage of oxygenated blood into the right side of the lesser circulation.

Case report

J. K., a 64-year-old man, was admitted to the National Heart Institute in January, 1966, because of severe congestive heart failure. A heart murmur had been noted at 22 years of age. He had been asymptomatic until 4 years prior to admission, when he noted the rapid development of cough, dyspnea, and edema. Administration of digitalis and dietary salt restriction resulted in improvement, and he remained relatively stable until 1 year before admission, when dyspnea, orthopnea, fatigue, and edema

From the Clinic of Surgery and the Cardiology Branch, National Heart Institute, Bethesda, Md.
Received for publication March 22, 1967.
*Address: Cardiovascular Diagnosis Section, Cardiology Branch, National Heart Institute, Bldg. 10, 7B 15, Bethesda, Md. 20014.

became progressively more severe. On admission, the pulse was 100 per minute and irregular the blood pressure 110/80 mm. Hg, and respirations 30 per minute. Th jugular veins were distended and exhibited prominent v wa e. Dullness and inspiratory ?les were noted at both lung bases. The heart was enlarged, nd right and left ventricular lifts nd systolic thrill t the apex were palpable The pulmonic component of the second heart sound as accentuated, there was a loud third heart sound and Grade 4/6 holosystolic murmur was audible t the apex. The liver was enlarged and moderate ankle edema was present. There was moderate enlargement of all cardia chambers and pulmonary vascular congestion on the chest roentgenogram and the electrocardiogram showed trial fibrillation and left entricular hypertrophy

At cardiac catheterization pressure in the pulmonary artery was 58/25 mm. Hg, right ventricle 58/3 mm Hg, right atrial mean pressure 5 mm Hg with aves of 8 mm. Hg The left atrial mean pressure was 24 mm Hg with waves of 70 mm Hg, left ventricle 100/12 mm Hg, and the aorta was 100/67 mm. Hg (Fig 1). Simultaneous recordings of pulmonary arterial and left atrial pressures revealed that left atrial pressure exceeded that in the pulmonary artery in late systole and early diastole (Fig 2). The cardiac index, determined by the Fick technique, as 1 10 L per minute per square meter P lmonary ascular resistance as 453 dynes-sec./cm The inhaled radioactive krypton (Kr[85]) test[a] with sampling in the pulmonary artery as positive, performed in duplicate ith indices of 15 and 25 per cent. With sampling from the right ventricle, the Kr[85] index was negative. The results of sequential determinations of oxygen saturation in the pulmonary arteries, right heart chambers, and vena ca ae are shown in Fig. 3 A step-up in oxygen saturation was found between the right ventricle and the main pulmonary artery and the saturation increased from 54 7 per cent immediately above the pulmonic alve to 61.6 per cent more distally in the main pulmonary artery to 68.4 nd 81 9 per cent in the proximal and distal portions of the right pulmonary artery respectively A left entricular cineangiogram demonstrated gross mitral regurgitation, with reflux of contrast material into the secondary tributaries of the pulmonary veins. The pulmonary artery did not appear to opacify however following left ventricular or aortic root injection of radiographic contrast material.

On March 25 1966 the patient underwent replacement of the mitral valve with Starr Ed ards prosthesis. The mitral alv leaflets were thickened and retracted and a central chorda tendinea to the posterior leaflet was ruptured The mitral annulus was markedly dilated. Although evidence of previous valvulitis was clearly present, it ppeared that the principal cause of the mitral incompetence was the ruptured chorda.

The patient experienced dramatic clinical improvement following operation. Postoperative cardiac catheterization, performed on September 20, 1966, showed a normal pulmonary arterial Kr[85] index of 2 per cent and no oxygen saturation step-up ithin the right heart or pulmonary arteries The pulmonary arterial pressure was 28/10 mm Hg the

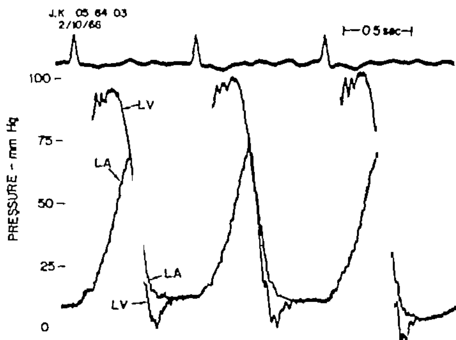


Fig 1 Simultaneously recorded left trial (*LA*) and left ventricular (*LV*) pressure pulses in patient J K., demonstrating marked ele tion of the left atrial v wave.

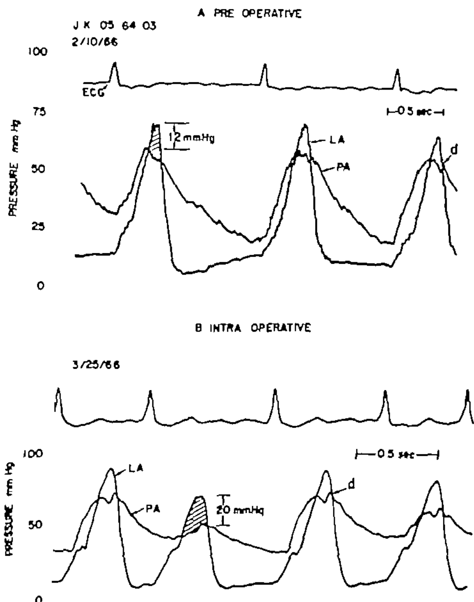


Fig 2 Simultaneously recorded left atrial and pulmonary arterial (*PA*) pressure pulses at preoperative catheterization (*A*) and at operation (*B*). Atrial fibrillation is present in both instances. The prominent positive deflection in the LA pressure pulse is the v wave. The reverse gradient between the LA and *PA* pressures are indicated by the shaded areas. The *d* represents the late systolic–early diastolic pressure deflection in the LA pressure pulse best shown on the intraoperative tracing

mean pulmonary arterial wedge pressure was 4 mm. Hg cardiac index determined by the indicator dilution technique was 2.21 L. per minute per square meter and the pulmonary vascular resistance was 291 dynes-sec cm $^{-5}$

Discussion

In the patient described the presence of an abnormally high level of inhaled Kr^{85} and a step-up in oxygen saturation at the level of the pulmonary artery could not be related by angiography or at operation to an abnormal communication between the systemic and pulmonary circulations. It was demonstrated however that (1) pressure in the left atrium exceeded that in the pulmonary artery in late systole and early diastole resulting in an upward deflection in the pulmonary arterial pressure pulse (2) oxygen saturation increased progressively with successively more distal

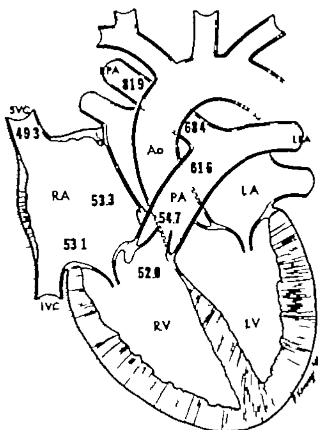


Fig. 3. Diagram depicting the per cent oxygen saturation values found at preoperative cardiac catheterization. *SVC*, superior vena cava; *IVC*, inferior vena cava; *RA*, right atrium; *RV*, right ventricle; *RPA*, right pulmonary artery; *LPA*, left pulmonary artery; *LV*, left ventricle; *Ao*, aorta.

pulmonary arterial sampling sites, and (3) evidence of a left-to-right shunt was not found at cardiac catheterization following the operative correction of severe mitral regurgitation. These observations allow the conclusion that the apparent left-to-right shunt preoperatively represented reflux of oxygenated blood retrograde through the pulmonary venous and capillary beds into the pulmonary arteries.

The pulsatile nature of pulmonary capillary blood flow in man has been recognized for some time and, moreover, present evidence suggests that inspired gas may be present normally in small branches of the pulmonary arterial tree immediately following inhalation. False-positive shunt tests have also been reported to occur in patients with and without mitral regurgitation with the use of the hydrogen inhalation technique, when a platinum-tipped electrode catheter was advanced into a small pulmonary arterial radicle or into the pulmonary arterial wedge position.[4] This finding has been ascribed to the retrograde diffusion of inspired hydrogen indicator from the alveoli and pulmonary capillary bed. Furthermore, false-positive nitrous oxide or Kr^{85} inhalation tests may occur if the pulmonary sample is aspirated from a catheter in or near the wedge position. In the patient described herein, it is postulated that severe mitral regurgitation accentuated this process, leading to positive Kr^{85} determinations in the main pulmonary artery. Moreover, there was also an increase in oxygen saturation in the proximal pulmonary arterial bed, a finding previously not described in patients with severe mitral regurgitation. Consonant with these observations is that retrograde filling of the small pulmonary venous

tributaries is one of the angiographic features of severe mitral regurgitation Since this reflux is probably not related entirely to dilatation of the pulmonary venous bed it is likely that some retrograde flow of upstream undyed blood takes place across the pulmonary capillary bed in certain patients with severe mitral regurgitation

Several factors may be of importance in determining the reflux of oxygenated blood into the pulmonary artery in such patients. The low distensibility of the left atrium and pulmonary venous bed characteristic of patients with severe mitral regurgitation resulting from the rupture of chordae tendineae usually results in marked elevation of the left atrial pressure during ventricular systole In addition regurgitation of a significant volume of oxygenated blood through the pulmonary capillary bed should require a relatively low pulmonary vascular resistance and in keeping with this, in the patient described the pulmonary vascular resistance was only moderately elevated Whether or not the elevated oxygen tension in the pulmonary arteriolar bed played a role in preventing further elevation of this resistance is, of course speculative Since the elevated oxygen content in the main pulmonary artery was not representative of mixed venous blood from the systemic circulation the systemic flow as determined by the Fick principle was somewhat overestimated Total pulmonary blood flow in this patient consisted of the right ventricular output plus the amount of reflux, the latter of which could not be quantitated Thus, in the determination of pulmonary vascular resistance the slightly underestimated pulmonary arteriovenous oxygen difference would tend to reduce the calculated value of pulmonary vascular resistance however the fact that reflux pulmonary flow was neglected would result in an overestimation of pulmonary vascular resistance

Summary

A patient with severe mitral regurgitation secondary to ruptured chordae tendineae is described in whom there was a positive pulmonary arterial Kr^{85} index and a step-up in oxygen saturation from right ventricle to pulmonary artery in the absence of an abnormal communication between the systemic and pulmonary circulations. It was demonstrated that left atrial pressure exceeded pulmonary arterial pressure in late systole and early diastole, and the oxygen saturation in the pulmonary arterial bed increased with progressively more distal sampling sites. Following operative correction of the mitral regurgitation cardiac catheterization showed a marked reduction in the left atrial pressure and the step-up in oxygen saturation in the pulmonary artery as well as the positive pulmonary arterial Kr^{85} inhalation test were abolished It was concluded that the preoperative evidence of left-to-right shunting represented reflux of oxygenated blood into the pulmonary artery resulting from the severe mitral regurgitation

REFERENCES

1 MacCallum W G and McClure, R D On the mechanical effects of experimental mitral insufficiency Bull. Johns Hopkins Hosp. 17:260, 1906

2. Levinson, D C Wilburne M Meehan J P and Shubin, H Evidence for retrograde transpulmonary propagation of the V (or regurgitant) wave in mitral insufficiency Am. J Cardiol. 2 159 1958

3 Braunwald E. Goldblatt, A., Long, R. T L., and Morrow A. G Krypton[85] inhalation test for detection of left-to-right shunts, Brit Heart J 24:47 1962.

4 Lee G de J and D Bois, A. B. Pulmonary capillary blood flow in man, J Clin. Invest 34 1380, 1955

5 Hirose T Schaffer A. I and Gasteazoro, G Experimental support for retrograde diffusion f om alveoli to pulmonary arteries, Dis. Chest 4 :511 1965

6 Gasteazoro, G., Hirose, T Stopak J Casala, J and Schaffer A. I The positive hydrogen test with platinum electrode in pulmonary wedge position, Am. J Cardiol. 12:240, 1963

7 Roberts, W C Braunwald, E., and Morrow A. G Acute severe mitral regurgitation secondary to ruptured chordae tendineae Clinical, hemodynamic and pathologic considerations, Circulation 33:58, 1966.

Review

Endomyocardial fibrosis in Uganda (Davies disease) Part II *

An epidemiologic, clinical, and pathologic study

Daniel H. Connor, M.D., C.M.
Krishna Somers, M.B., Ch.B., M.R.C.P.
Michael S. R. Hutt, M.D.
William C. Manion, M.D.
Paul G. D'Arbela, M.B., B.Ch., M.R.C.P. (Edin.)
Washington, D. C., and Kampala, Uganda

Microscopic findings. The most striking microscopic changes were in the connective tissues of the endocardium and the inner portion of the ventricular myocardium. As seen under the light microscope, the normal ventricular mural endocardium is composed of a single layer of flat cells supported by a thin layer of loose connective tissue. In the EMF hearts, however, the connective tissues of the endocardium and adjacent myocardium were swollen and in sections stained with hematoxylin and eosin appeared as expanded faintly eosinophilic ground substance. With Movat's pentachrome stain, the interrelationship of mucin, collagen, elastica, fibrin, and muscle was readily defined.

ENDOCARDIUM. The swollen connective tissues of the endocardium and underlying myocardial interstices contained excessive acid mucopolysaccharide (AMP) (Color Plate I, middle right; Color Plate II, Fig. 1, top right and bottom left; Fig. 9, top and bottom right). The amount of AMP varied from a faint trace in some areas to larger pool-like deposits in others. In 6 hearts (Nos. 1 to 5 and 7) fibrin covered and merged with the underlying AMP (Fig. 3, top right). Although the connective tissues of endocardium, myocardium, and epicardium of the various chambers contained some AMP, the greatest deposits were in the endocardium of the hearts of the patients with short clinical histories. Conversely, AMP was less abundant in the hearts of those with longer histories and severe scarring. Stellate and round mesenchymal cells were prominent in the AMP deposits (Fig. 6, bottom right; Fig. 8, middle right; Fig. 9, top right). Some of

From the Geographic Pathology Division, Armed Forces Institute of Pathology, Washington, D. C. 20305, and from the Departments of Medicine and Pathology, Makerere Medical School, Kampala, Uganda.
This work was supported in part by research grant, Project Nos. DA-MD-49-193-63-G101 and 3A014501B71Q, from the Medical Research and Development Command, U. S. Army, Washington, D. C., and in part by the World Health Organization.
*Part I of this study appeared in the November 1967 issue of the Journal.

these cells were swollen with intracytoplasmic AMP and in some sections, the mesenchymal cells appeared to be disintegrating and releasing AMP (Color Plate II top left Fig 6 bottom right) Increased AMP was also evident in the tricuspid and mitral valve leaflets. Each heart had some fibrous thickening of the endocardium although the amount varied from heart to heart and from area to area in the same heart In some areas where AMP thickened the endocardium capillaries and fibroblasts had penetrated from below (Color Plate I middle right Fig 3 top right) Within this organizing zone AMP was diminished and there were large numbers of Anitschkow myocytes, other histiocytes, lymphocytes and scattered plasma cells, polymorphonuclear leukocytes, and eosinophils. In some involved areas the full thickness of swollen endocardium was vascularized (Fig 1 top right) In early lesions there were thin strands of hyalinized scar tissue between the myocardium and the overlying organizing mucin and in the older lesions the entire endocardium was composed of hyalinized collagen intermixed with elastica and a few smooth muscle fibers (Fig 5 top right Fig 12 bottom left) The endocardial scars were anchored to the myocardium by tracts of fibrous tissues, which penetrated into the trabecular spaces Four hearts had foci of calcification in the endocardial scars (Fig 12 right)

VESSELS There were similar changes in the cardiac vessels. When the clinical history was short AMP and mesenchymal cells, many of which contained AMP were prominent in the walls of the subendocardial arterioles (Color Plate I bottom right Fig 1 bottom right) AMP separated the muscle fibers of the media thickened the wall and narrowed the lumen (Fig 3 bottom left) In many arterioles the intimal cells had proliferated had further compromised the lumen and had occasionally occluded it. The arterioles immediately beneath the thickened endocardium were the vessels most severely involved but there were less severe changes in other cardiac vessels, including the subepicardial vessels and the main coronary arteries and veins (Fig 3 middle right Fig 10 middle right) In the hearts of those with longer clinical courses, the muscularis of the subendocardial arterioles was replaced by a mixture of hyalinized collagen and elastica (Fig 4 top right Fig 5 bottom left and middle Fig 7 bottom left) In addition many of the cardiac vessels were surrounded by broad tracts of fibrous tissue (Fig 5 bottom left and bottom middle) The gross beading of the epicardial vessels noted in one heart

Fig 5 Top left There is fibrosis of the posterior wall of the left ventricle with fibrosis and contraction of the posterior mitral leaflet (upper arrows) The fibrous tissue tapers to grossly normal endocardium around the base of the posterior papillary muscle There is an isolated apical endocardial scar (bottom arrow) (Heart No. 6 mitral valve, × 0 4 AFIP Neg 66-7390)

Top right This is section through the left ventricular apex see Color Plate II bottom right. The endocardial scar is composed of elastica and smooth muscle In addition there is subendocardial scarring (arrows). Within the scar there are foci of collagen degeneration. In these areas the collagen bundles are separated and swollen and have undergone tinctoral change. In addition there is an accumulation of AMP Anitschkow myocytes, and mesenchymal cells. (Heart No. 6 apex of left ventricle Movat, × 56 AFIP Neg 65-2145)

Middle left In addition to the left-sided scars there is fibrous obliteration of the right ventricular apex producing a notch along the right border (arrow). (Heart No. 6 pulmonary valve × 0 4 AFIP Neg 66-7391)

Middle right This is section through the posterior wall of the left ventricle. The superficial portion of the scar (*A*) is composed of collagen elastica and smooth muscle Deeper at (*B*), the collagen and elastic fibers are separated by AMP The underlying scar (*C*) is inactive and is probably an organized microinfarct (Heart No. 6, posterior wall, left ventricle, Movat × 40, AFIP Neg 66-1653.)

Bottom left This is an oblique section of a fibrotic arteriole beneath the left apical scar There is perivascular fibrosis and reduplication of the elastica. Only few fragments of smooth muscle remain in the wall. (Heart No. 6 left ventricular apex, Movat, × 105 AFIP Neg 66-4062.)

Bottom middle This is another damaged arteriole just distal to a bifurcation Perivascular fibrosis and scarring of the vessel wall are seen (Heart No. 6 intraventricular septum Movat × 170 AFIP Neg 66-1652)

Bottom right In addition to disruption of the deep endocardial collagen, there were occasional foci of collagen degeneration within interstitial scars The collagen at the tips of the arrows is coarse, fragmented and discolored. (Heart No. 6 interventricular septum Movat, × 180 AFIP Neg 66-1651)

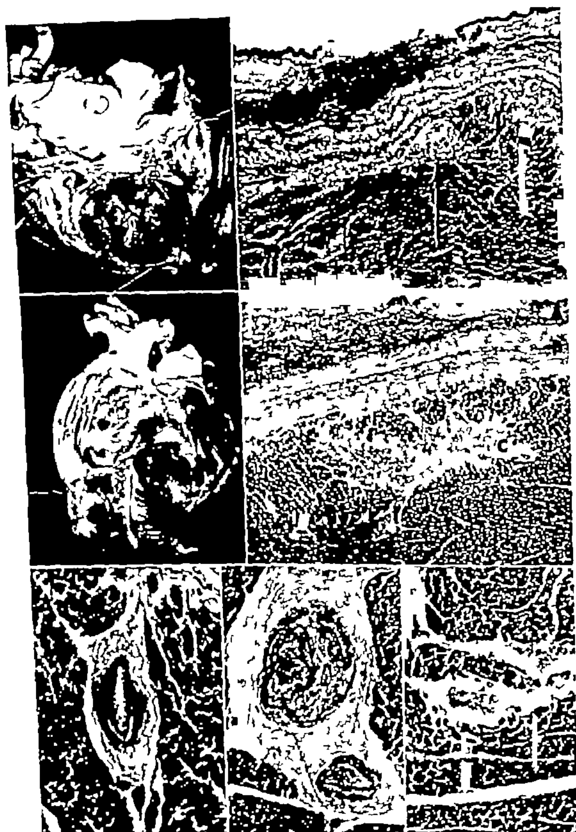


Fig. 5 For legend see opposite page.

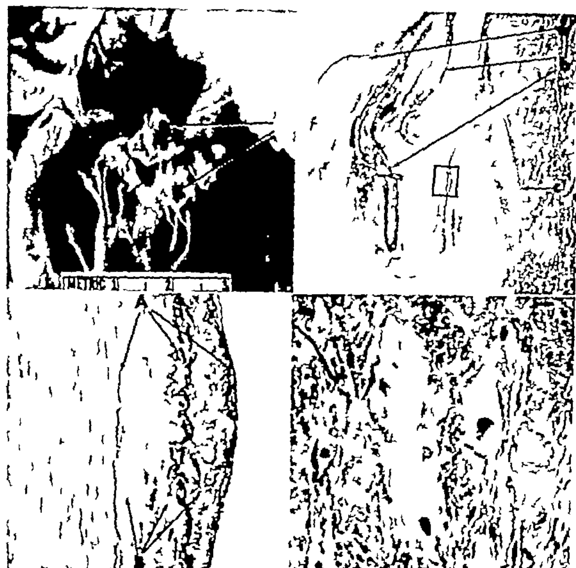


Fig. 6. Top left. In this heart there were characteristic lesions in the left ventricle (Fig. 7), but in the right ventricle the pattern was unusual in that there tended to be focal scarring, rather than a single thick scar at the apex, tapering toward the tricuspid ring and outflow areas. This is a view of the medial leaflet of the tricuspid valve. The leaflets are normal, and the chordae tendineae are not shortened or fused, but 2 of them are surrounded by fibrotic nodules. The central portion of the leaflet has been reflected up to show these nodules (upper arrow) and the facets on the mural endocardium that oppose them (lower arrow). (Heart No. 7, tricuspid valve, × 1.3. AFIP Neg. 66-7393.)

Top right. This is an enlargement of one of the nodules, and it shows slightly edematous but otherwise normal valve leaflet (a) over 2 chordae tendineae (b), which are fused by the accretion of fibrous tissue. This lesion opposes a fibrotic plaque ( ) on the mural endocardium. Although both lesions are mostly hyalinized scar tissue, the opposing surfaces are built up by layers of fibrin and acid mucopolysaccharide. (Heart No. 7, medial leaflet of tricuspid valve, Movat, × 8, AFIP Neg. 66-7394.)

Bottom left. This is an enlargement of the rectangular area outlined in the preceding photograph to show alternating layers of fibrin (A) and mucinous connective tissue (B). (Heart No. 7, tricuspid nodules, Movat, × 80, AFIP Neg. 66-7395.)

Bottom right. This is an enlargement of the mucinous matrix between the layers of fibrin. There is AMP in and between the swollen mesenchymal cells. The largest mesenchymal cells may be degenerating. (Heart No. 7, tricuspid nodule, Movat, × 395, AFIP Neg. 66-7396.)

consisted of nodules of hyaline scar tissue in the wall of the vessels. In 2 hearts, the pericardial lymphatics were distended with AMP (Fig 7 bottom right)

MYOCARDIUM When the clinical course was short, the myocardial interstices contained excessive AMP The largest deposits were in the areas adjacent to the thickened endocardium and here, AMP widely separated the muscle fibers. The middle and outer thirds of the myocardium were less severely involved but there were random traces of AMP between individual myofibers throughout all portions of the myocardium (Fig 1 lower left Fig 5 middle right Fig 8 middle right) As in the endocardium and vessels, the interstitial AMP resolved as fibrous tissue (Color Plate II bottom right Fig 1 bottom right Fig 5 bottom right Fig 9 top and bottom right) In 7 hearts (Nos. 1 to 5 11 and 16) there were sharply outlined foci of myocardial degeneration. These were situated around or adjacent to damaged arterioles, and most were in the subendocardium (Color Plate I top right Fig 2 top right and bottom left) Within these areas, the myocardial fibers had vanished and this gave the area a punched-out appearance. These areas had reached various stages of organization and in the hearts from patients with the longest clinical histories, they had resolved as stellate scars (Fig 5 middle right) These lesions are probably small areas of ischemic myocardial necrosis. They did not contain AMP

COLLAGEN NECROSIS There were peculiar foci of necrosis in the endocardial collagen. These were circumscribed foci of swollen collagen fibers that had become granular and had lost their fibrillations and some of their birefringence. The collagen was intensely eosinophilic and had less affinity for aniline blue. In Movat-stained sections, the collagen absorbed woodstain scarlet which imparted a bright orange-red color in contrast to the yellow of the saffron-stained normal collagen (Color Plate II top left and right middle left and right and bottom right Fig 5 top right and bottom right Fig 7 top right and middle left and right Fig 8 middle right Fig. 10 middle left) There were small amounts of AMP around and between the altered collagen fibers stellate and round mesenchymal cells were prominent within this AMP The elastic and collagen fibers that had surrounded the degenerating foci were displaced and this gave some lesions an expanded or exploded' appearance. These lesions were present in 15 of the 16 hearts (they were absent in the heart of the patient (No. 1) with the shortest clinical history) Dense endocardial scar had not yet formed in this heart. These peculiar necrotic foci were situated in the scar tissue at the junction of the thickened endocardium and underlying myocardium. In 3 hearts (Nos. 5 to 7) there were similar foci of necrotic collagen in the scars of the myocardial interstices. Each heart had active lesions. None could be described as "burnt out."

INFECTIOUS AGENTS In one heart (No. 9) there was a single microfilaria between two myofibers in a section through the apex of the right ventricle. This patient had 1,500 ml. of pericardial fluid at autopsy The microfilaria looked viable, had provoked no inflammatory reaction and was morphologically consistent with *Dipetalonema perstans* the most common filaria that infects man in Uganda *D perstans* is thought to be an innocent parasite. We found no other microorganisms nor did we find microabscesses, granulomas, or other evidence of infection.

OTHER ORGANS Microscopic fibrin emboli, which presumably originated from the fibrin plaque in the left ventricle, had produced minute infarcts in the testis and pancreas (No. 1) In another subject (No. 2) the coronary vein was partially obstructed by an organizing thrombus (Fig 3 bottom right) There were no other emboli. We found no significant connective tissue alterations outside the heart. Sections of all vital organs including skin and subcutaneous tissues as well as skeletal muscle, articular cartilage lymph nodes, thymus, gonads, bone, gallbladder stomach and intestine failed to reveal excessive interstitial AMP or foci of collagen degeneration

There was acute and chronic passive congestion of the lungs in all 16 patients, as well as ascites in 12 patients. In 2 (Nos. 13 and 15) there was bronchopneumonia in the dependent portions. Four (Nos. 9

11, 13 and 14) had marked centralobular congestion of the liver and in one (No. 15) this had progressed to cardiac cirrhosis. These 5 subjects had severe fibrotic changes in the right ventricle. In one (No. 1) there were miliary tubercles containing acid fast bacilli in the liver and abdominal lymph nodes. None of the others had active tuberculosis, but there were massive bilateral pleural adhesions in two patients (Nos. 7 and 12) and one of these (No. 7) had been treated for proved pleural tuberculosis. The livers and spleens of four patients (Nos. 4, 10, 13 and 15) contained clumped malaria pigment but in none of these was there evidence of active malaria. Four patients had hookworm infections (Nos. 1, 3, 15 and 16), one patient also had ascariasis (No. 1) and another tapeworms (No. 15). One patient had tapeworms and ascarids (No. 9) and another tapeworms alone. The kidneys in one patient (No. 11) had advanced changes of pyelonephritis.

Discussion

Our findings reveal that endomyocardial fibrosis in Uganda (Davies' disease) is a disorder of the cardiac connective tissues. Following some undefined insult, acid mucopolysaccharide (AMP) swells the connective tissues of the endocardium and inner myocardium. Blood vessels and fibroblasts then grow into the swollen connective tissues and convert the involved area to scar tissue. AMP is a component of normal connective tissues but in the normal heart it is present in such small quantities that, apart from the valves, it is usually not evident in routine sections. There is some increase in interstitial AMP in many of the myocarditides, but the excessive deposition of AMP in EMF is a fundamental and possibly unique change. We also believe that the foci of collagen necrosis are focal manifestations of a diffuse change in the cardiac areolar connective tissue and that these necrotic foci not only are characteristic of EMF but may be diagnostic. The fact that there were both active and chronic lesions in each heart supports the clinical observation that EMF is a continuously progressive cardiopathy. The combination of mucinous swelling of the cardiac ground substance and focal nonsuppurative disintegration of collagen suggests to us that hypersensitivity may be the underlying mechanism in EMF.

One patient (No. 13) had a rapidly progressive carditis and fever of 4 weeks' duration; at autopsy the heart was dilated, but there was no gross endocardial scarring. Microscopically, however, there was fibrosis of the endocardium (up to 0.1 mm thick) in the recess behind the posterior mitral leaflet and in this scar there were foci of collagen necrosis characteristic of EMF. Thus, as deduced by Edington and Jackson,[14] our study reveals that in EMF

Fig. 7. *Top left.* This shows one of the characteristic lesions of the left ventricle. There is white fibrous thickening of the endocardium behind the posterior leaflet which extends down the posterior wall, and becomes thinner around the base of the posterior papillary muscle. The fibrosis of the apex is not shown. (Heart No. 7, mitral valve, × 0.96, AFIP Neg. 66-7397.)

Top right. This is from section taken at (a) in the previous picture. At either side of the central nodule, the endocardial scar is composed of compact collagen and elastica but, in the center, the scar is "exploded" by AMP. This process is centered at the arrow tip and involves the *full thickness* of the endocardial scar. (Heart No. 7, posterior wall of left ventricle, Movat, × 42, AFIP Neg. 66-7398.)

Middle left. This is from a section of the left atrium at (b) in the picture above. This field is located at the junction of the thickened endocardium and myocardium (for orientation see Color Plate II, middle right). The lesion at the arrow tip is a focus of degenerating collagen. AMP separates the connective tissue fibers, and at the arrow tip the collagen bundles are orange, coarse and without normal fibrillations. (*Heart No. 7, left atrium,* Movat, × 265, AFIP Neg. 66-7399.)

Middle right. This is from the same slide as that in Color Plate II, middle right, and is a higher magnification of the largest lesion. (Heart No. 7, left atrium, Movat, × 330, AFIP Neg. 66-7400.)

Bottom left. This is a section through the left apex. The trabecular muscle is surrounded by endocardial scar. In addition, fibrous tissue has thickened and surrounded the contained arteriole. (Heart No. 7, left ventricular apex, Movat, × 50, AFIP Neg. 66-7401.)

Bottom right. This is pericardium along the right border of the heart. The adipose tissue is congested and the dilated lymphatic contains AMP. (Heart No. 7, pericardium, Movat, × 35, AFIP Neg. 66-7403.)

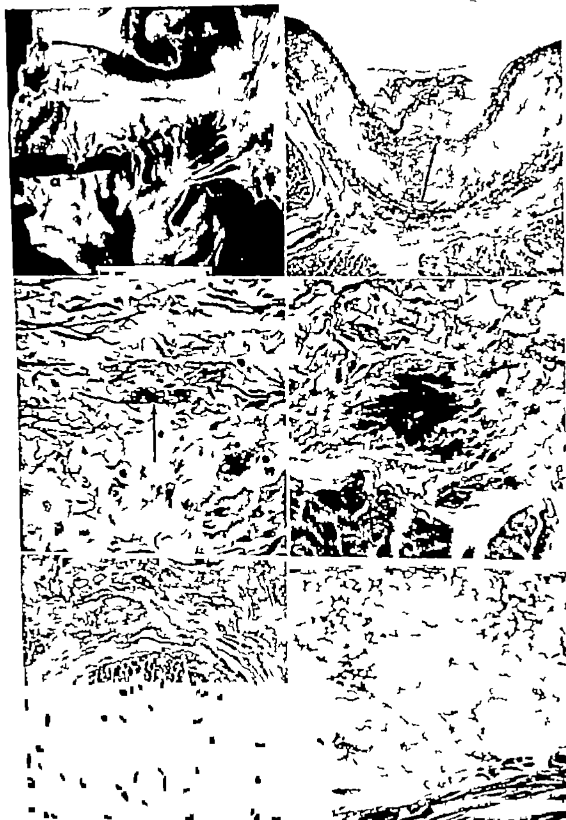


Fig. 7 For legend see opposite page.

cardiac dilatation and hypertrophy may precede gross endocardial scarring

The consistent location of the gross lesions remains unexplained Microscopically however the gross lesions are only accentuations of a more diffuse process. *Eddies and sluggish flow behind the posterior mitral leaflet and at the apices may* cause excessive deposition of fibrin and hence larger lesions at these sites.

Although our findings help define EMF and point to hypersensitivity as the underlying mechanism the cause remains obscure That EMF is a variant of rheumatic heart disease (RHD) has been proposed *for morphologic reasons,*[33,34] and recently Shaper[35,36] *has assembled epidemiologic* clinical immunologic and pathologic evidence that tends to relate the 2 diseases. From his analysis of the autopsy records at Mulago Hospital he found that the low incidence of RHD in the Rwanda was partially balanced by the high incidence of EMF *He also calculated from autopsy records that the incidence of hearts containing lesions of both RHD and EMF was* at least 4½ times the chance occurrence of the 2 diseases in a single patient In our study we found as did Shaper that the Rwanda were predisposed to EMF but we could not document lesions of both diseases in the same heart. Further evaluation of this must await demonstration of both disease processes in the same heart

EMF and RHD are both acquired and in many cases progressive and fatal Both cause endocardial scarring (valvular and mural respectively) both cause abnormalities of atrioventricular valves, both afflict children and young adults and both are characterized by swelling of the cardiac "*ground substance and by foci of collagen* necrosis. Is one disease a variant of the other? Rheumatic fever is generally believed to be causally related to infection by a Group A beta-hemolytic streptococcus but as pointed out by the committee to revise *Jones criteria the boundaries of RHD* are indefinite and RHD may be impossible to distinguish from other diseases. *It is not surprising therefore* that rheumatic heart disease in Uganda has been confused with EMF At autopsy however typical examples of RHD and EMF are distinct and the examples we studied have convinced us that they are 2 different diseases.

A number of features serve to differentiate RHD from EMF Established EMF is seen at a younger age than established RHD In fact the chronic valvular lesions of rheumatic heart disease are rarely if ever seen at autopsy during the first decade. Yet well-established EMF (scarring focal calcification contraction of the right ventricle *and tethering of the atrioventricular valve leaflets) is common in* the first decade. Our youngest patient had

---

Fig. 8 Top left This 26-year-old Rwanda woman died after a clinical course characterized by congestive heart failure for 15 months. *Grossly there were 3 endocardial scars, one in each of the 3 characteristic sites. The scar in* the right ventricle produced a contraction notch along the right border (arrow). (Heart No. 8, anterior view × 0.5 AFIP Neg 66-7403)

Top right The scar in the right ventricle shown here was maximal at the apex (*c*) and extended up partially surrounding the papillary *muscle* (*b*), and encroached on the chordae tendineae The leaflets were not involved The right atrium was dilated and the appendage thrombosed ( ). (Heart No. 8, tricuspid valve, × 0.5 AFIP Neg 66-7404)

Middle left The right ventricular *outflow was dilated* and hypertrophied *In addition there was an oval* 1.5 *cm.* scar on the septal endocardium just beneath the pulmonary ring (arrow). Although this scar was in an atypical site the microscopic organization was identical to that of the large scars (Heart No. 8, pulmonary valve × 0.5 AFIP Neg 66-7405)

Middle right *This is the focally* thickened endocardium seen grossly in the preceding photograph. There are degenerating collagen bundles at (*a*) and AMP in the endocardium and around the muscle bundles at (*b*). (Heart No. 8 endocardium, right ventricle Movat, × 180 AFIP Neg 66-1647)

Bottom left: This shows the scar on the *posterior wall of the* left ventricle It has contracted the posterior mitral leaflet to a fibrous ridge ( ). The endocardium around the posterior papillary muscle is spared (*b*) but there is a broad apical scar (*c*). (Heart No. 8 mitral valve, × 0.5 AFIP Neg 66-7406.)

Bottom right. This is a view of the mitral valve *from the atrial aspect. Water was forced into the left ventricle through the aortic valve The fibrotic posterior leaflet at* (*a*) fails to form a seal with the anterior leaflet Virtually the entire orifice, in fact, is filled with the anterior leaflet. A regurgitant stream is seen at (*b*). Clinically the patient *had mitral insufficiency (Heart* No. 8, mitral valve, × 1.2 AFIP Neg *66-7407*)

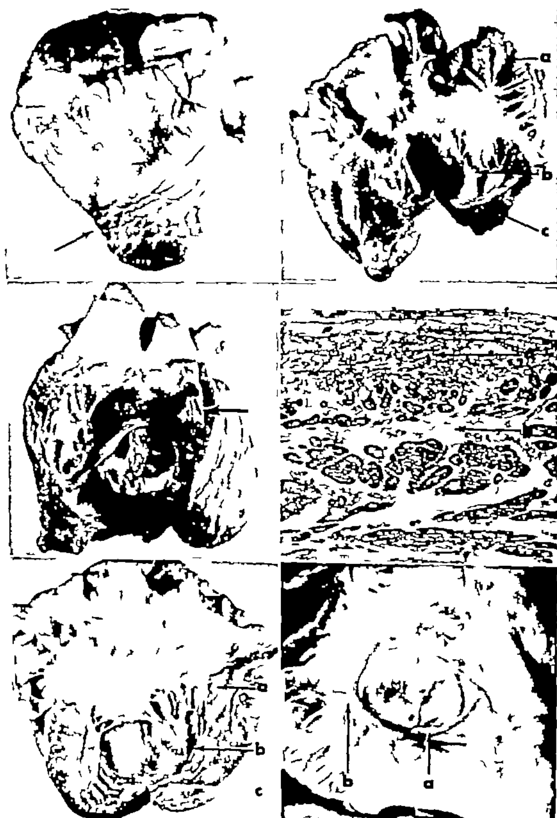


Fig 8 For legend see opposite page.

advanced EMF of the right ventricle when he died at 4 years of age and a more recent patient (not included in this series) died with advanced disease at 2 years of age. Patients with chronic RHD often have multiple stenotic lesions of the valves EMF does not produce valvular stenosis. In established RHD the leaflets and chordae tendineae are thickened and shortened the commissures are adherent and scarred and the valve leaflets and the base of the valves may be focally calcified and even ossified In EMF however the leaflets and chordae are only slightly thickened if at all and the commissures remain unscarred The aortic and pulmonary valves are not involved and while the chordae tendineae and the papillary muscles of the tricuspid valve may be *scarred in EMF the leaflets are not affected*

The major clinical criteria for the diagnosis of RHD are carditis, polyarthritis, chorea subcutaneous nodules, and erythema *marginatum*[47] None of these was present in any of the 16 patients with EMF Of the minor criteria fever was common and arthralgia noted in one patient The bulky fibrin thrombi and the fibrous contraction of the right ventricle common in EMF are not features of RHD Microscopically myofiber degeneration is a more prominent feature of EMF than of RHD The foci of collagen necrosis in EMF are not features of RHD and they differ morphologically from Aschoff bodies, which are the characteristic lesion of RHD Aschoff bodies resemble the foci of collagen necrosis of EMF in that they contain fibrinoid The fibrinoid in the EMF lesions, however persists into the late phase whereas the fibrinoid in the Aschoff body is seen only in the acute phase as it is phagocytosed and replaced in later stages by fibrous scar Active phagocytosis was found in one EMF heart Another distinguishing point is that the necrotic foci in EMF are associated with a less pronounced cellular infiltrate than Aschoff bodies the latter contain a prominent infiltrate of lymphocytes and Aschoff cells (Anitschkow myocytes) Furthermore the majority of EMF necrotic foci were in the scar at the endomyocardial junction but Aschoff bodies develop in the unscarred loose perivascular connective tissues of all portions of the heart In this study we found no evidence of connective tissue disturbance outside the heart but RHD is a generalized disorder involving the connective tissues of other organs.

In considering the possibility of specific etiologic agents Sternon and associates questioned the role of filariasis, and more recently Ive and Brockington and Brockington and Willis[8] have related the filarial infections to EMF The patient reported by Brink and Weber[44] had onchocerciasis. In Uganda loiasis is rare and the areas of endemic onchocerciasis and bancroftian filariasis do not correspond to the recognized areas of EMF Another filaria *Dipetalonema perstans* is ubiquitous in Uganda as well as in tropical Africa generally and in one heart we found a single microfilaria consistent with this species.

Fig 9 Top left A 12 year-old Rwanda girl died after chronic pericardial effusion and congestive failure for 4 years. She had repeated pericardiocenteses. At autopsy there were scattered nodules of brown pigment (lipofuscin) on the pericardium and there was a broad pericardial adhesion along the right ventricular border In addition the contraction deformity or notch is seen along the right border (arrow). (Heart No. 9 anterior aspect × 0.7 AFIP Neg 66-7408)

Top right: This is a section through the wall of the right ventricle at the level of the arrow in the bottom left photograph Stellate mesenchymal cells containing AMP and extracellular AMP have thickened the endocardium (Heart No. 9 right ventricle Movat × 305 AFIP Neg 66-1446)

Middle left: Maximum right ventricular scarring is at the apex. It tapers up over the papillary muscles to reach the chordae tendineae The right atrium and appendage are dilated, and fibrous plaque fills the tip of the appendage (Heart No 9 tricuspid valve × 0.5 AFIP Neg 65-1661)

Bottom left: The thickness of the endocardial scar tapers in the outflow tract to merge with normal endocardium just below the pulmonary valve There is some dilatation and hypertrophy of the pulmonary conus (Heart No. 9 pulmonary valve × 0.5 AFIP Neg 65-1660)

Bottom right This section is from the apex of the right ventricle at the level of the arrow in the photograph at middle left. The venous channel is surrounded by connective tissue swollen by AMP and containing prominent mesenchymal cells. (Heart No. 9 right ventricle Movat, × 80 AFIP Neg 66-1449)

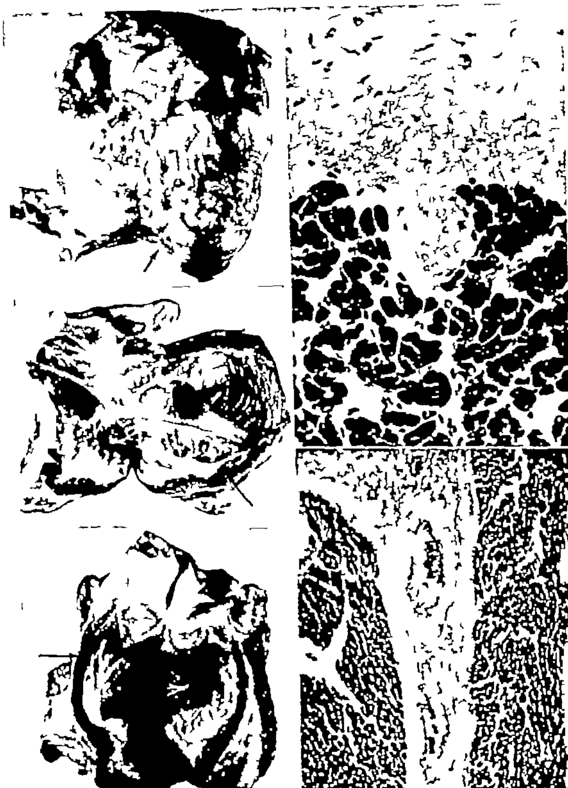


Fig. 9 For legend see opposite page.

Furthermore there were large numbers of *D perstans* microfilariae in the pericardial aspirates of a patient with EMF not in our study [71] Six patients had a persistent eosinophilia but the significance of this remains obscure Although we can find no epidemiologic evidence to indicate that filariasis causes EMF we cannot deny that EMF could be a hypersensitivity reaction to a filaria. Current studies to test this possible relationship will be of interest [72, 73]

Malnutrition seems an unlikely factor in the genesis of EMF Patients with severe undernutrition including starvation and kwashiorkor are seen regularly in the wards or at autopsy at Mulago Hospital During the study 5 adults died of starvation but the hearts of these patients showed no gross or microscopic evidence of EMF In addition we studied the hearts of 5 fatal cases of kwashiorkor and none of these had the changes we found in EMF Conversely only 2 patients in this series of 16 had evidence of undernutrition at autopsy Plantain a staple of Ugandans in the Kampala area is rich in 5-hydroxytryptamine and speculation about the causal role of plantain in EMF followed the recognition of carcinoid heart disease This seems unlikely for several reasons. The Ganda ingest more plantain than the Rwanda, yet the Ganda are not predisposed to EMF Furthermore the lesions in EMF are very different from those of carcinoid heart disease [73] McKinney and Crawford however fed guinea pigs a high plantain diet and found small foci of fibrotic endocardial thickening and minute foci of endocardial fibrin These observations are difficult to relate to EMF for a number of reasons. In many human hearts small foci of endocardial thickening occur near tendinous insertions, in the recesses of the valve leaflets and on endocardial prominences of the muscular trabeculae. Some of these are anchoring fibrous tissue and others may be residues of old inflammations, but they can be found in a great number of hearts that are carefully examined. Furthermore none of the animals, that McKinney and Crawford examined had gross lesions heart failure or lesions that would conform to the process we have found in the hearts with EMF Also Ganda infants, dying of a high plantain and low protein diet (kwashiorkor) do not have EMF We know of no current evidence to support the view that malnutrition is a causal factor in EMF

In support of an autoimmune mechanism Van Der Geld and associates[73, 74] used fluorescent immunoglobulin staining and found " fibrin deposits in heart, kidney spleen liver pancreas thyroid lung " and a high incidence of circulating antibodies of the heart With our methods we found abundant fibrin in the endocardium of our EMF hearts, but we did not find it throughout the myocardium as did they nor did we find fibrin in other organs. While EMF may be the consequence of an autoimmune reaction (and the high

Fig 10 Top left A 6-year-old Rwanda boy died after a 1 month illness characterized by severe dyspnea, ascites, and peripheral edema. At autopsy the heart was dilated and globular At the apex of the right ventricle there was minimal fibrosis around some of the trabeculae and in the intratrabecular spaces (arrow) (Heart No. 10 right ventricular apex, × 3 5 AFIP Neg 66-7409)

Top right. In the left ventricle there was broad flat scar at the apex and another scar behind the posterior mitral leaflet This tethered the leaflet and its attached chordae to the posterior wall (Heart No. 10 mitral valve × 0.76, AFIP Neg 66-7410)

Middle left This section of endocardium was taken through the left ventricle at (*a*) in the photograph at top right. The dark focus at the tip of the arrow is degenerating collagen. The surrounding connective tissues are swollen and separated by mucin and mesenchymal cells see Color Plate II top left. (Heart No. 10 left ventricle × 145, AFIP Neg 66-1459)

Middle right: This is vein beneath the epicardium in the posterior wall of the left ventricle Fibrous tissue lines the vessel and partially occludes the lumen. The collagen and muscle fibers of the wall of the vein are separated by mucin. (Heart No 10 left ventricle Movat × 63 AFIP Neg 66-1457)

Bottom left A 35-year-old Rwanda woman died after 2 years of repeated attacks of congestive heart failure This is the anterior aspect of the heart showing the characteristic right border notch (arrow). (Heart No. 11 anterior view × 0 46, AFIP Neg. 66-7411)

Bottom right: The right ventricle has been opened along the posterior interventricular septum There is fibrotic obliteration of the apex. (Heart No. 11 right ventricle × 0 46, AFIP Neg 66-7412.)

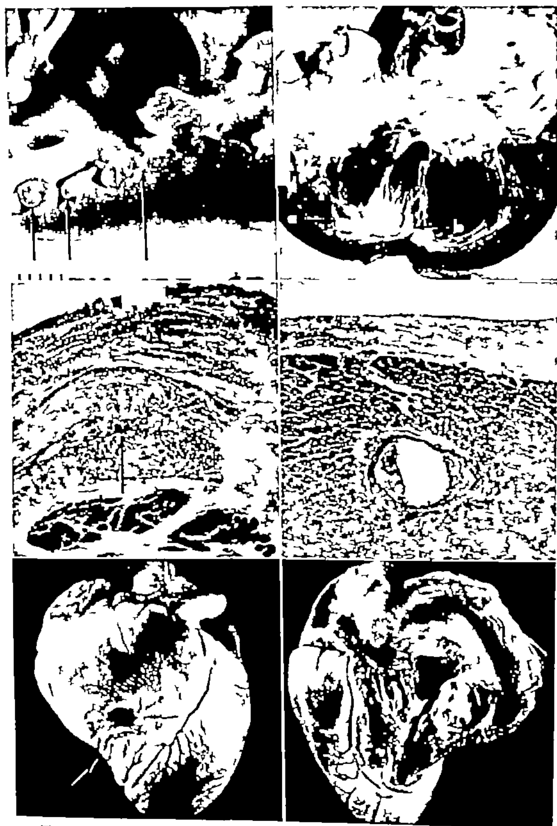


Fig. 10 For legend see opposite page.

serum gamma globulins found in this series are consistent with an autoimmune disorder) we did not find large numbers of immunologically competent cells at the endomyocardial junction nor did we find evidence of a generalized process.

Parry and Abrahams[17] have speculated about a vector-born virus because the initial illness in some of their patients began during the rainy season. No seasonal incidence was evident in our patients, and although a viral infection could cause myocardial degeneration it is an unlikely explanation for the disruption and focal degeneration of the cardiac connective tissues and vessels. Fever as an historical precedent is difficult to evaluate but the fever may represent an initiating illness.

In Uganda Rwanda immigrants are predisposed to EMF whereas the Ganda are not. Hypersensitivity to an herb or vapor taken or used by the Rwanda as a tribal medicine or fetish would conform to the known facts, including the preponderance of female subjects of reproductive age. Tribal medicines are guarded secrets, however and attempts to relate these to EMF have as yet been unrewarding. Language barriers and superstitions also contribute to these difficulties. Ingestion of some South African plants of the family Rubiaceae causes a fatal ovine heart disease characterized by focal myocardial necrosis, capillary engorgement chronic inflammatory cell infiltrates, and fibrosis. This is *gousiekte* (sudden death) well known to the veterinarians of South Africa.[71] There are differences between gousiekte and EMF but it is an interesting fact that some indigenous African plants cause fatal mammalian heart disease.

Summary

Endomyocardial fibrosis in Uganda (Davies disease) is a common type of fatal heart disease in the autopsy population at Mulago Hospital. During this study endomyocardial fibrosis caused 25 per cent (16/65) of deaths from intrinsic heart disease. It showed a striking and unexplained predilection for the immigrant Rwandans, but spared the large local indigenous tribe the Ganda. Clinically the patients had a sudden or insidious onset of failure of one or both ventricles, which proved fatal over a period of days weeks months, or years. At necropsy there were mural endocardial lesions at one or more of three sites—the apex of the right ventricle the posterior wall of the left ventricle and the apex of the left ventricle. In the early stage the cardiac connective tissues, especially those of the endocardium were swollen with acid mucopolysaccharide (AMP) and covered by a layer of fibrin. In later lesions the involved areas had resolved as hard white scars composed of collagen and elastica. There were peculiar and we believe characteristic foci of collagen necrosis in the scar tissue at the endomyocardial junction

Fig. 11 Top left: In this heart the right border notch is prominent (see arrow) and is accentuated by dilatation of the outflow tract. (Heart No. 14 anterior view × 0.5 AFIP Neg 66-7414.)

Top right: This shows fibrous obliteration of the right ventricular apex. The apical scar has covered the papillary muscles up to the chordae tendineae. The tricuspid ring and the right atrium and its appendage are dilated. (Heart No. 14 tricuspid valve × 0.4 AFIP Neg 66-7415.)

Middle left: The outflow tract of the right ventricle is dilated and hypertrophied but free of endocardial scarring. The pulmonary valve is normal. (Heart No. 14 pulmonary valve × 0.5 AFIP Neg 66-7416.)

Middle right: In the left ventricle the endocardium of the apex is free of gross scarring but a portion of the posterior leaflet of the mitral valve is obliterated and fixed to the posterior wall of the left ventricle by fibrous tissue (arrows). The commissures are not scarred or fused. The chordae tendineae of the anterior leaflet are not grossly scarred and the endocardium of the left atrium is smooth and glistening. (Heart No. 14, mitral valve × 0.5 AFIP Neg 66-7417.)

Bottom left: This heart was inflated before dissection. This is the posterior aspect and shows the greatly dilated right atrium. The protrusion at (A) is the coronary sinus. Severe contraction of the border of the right ventricle is seen at (B). (Heart No. 12 posterior view × 0.4 AFIP Neg 66-7418.)

Bottom right: The shallow floor of the contracted right ventricle is covered with scar tissue. There is plaque of calcium at the tip of the arrow and the saccular enlargement below this is a compensatory dilatation and hypertrophy of the pulmonary conus. The dilatation of the tricuspid ring with fixation of the tricuspid leaflets has made a common chamber of the right atrium and ventricle. The left ventricle is at the right. Scar tissue surrounds the papillary muscles and the trabeculae carneae. (Heart No. 12, cross section through ventricles, × 0.7 AFIP Neg 66-7419.)

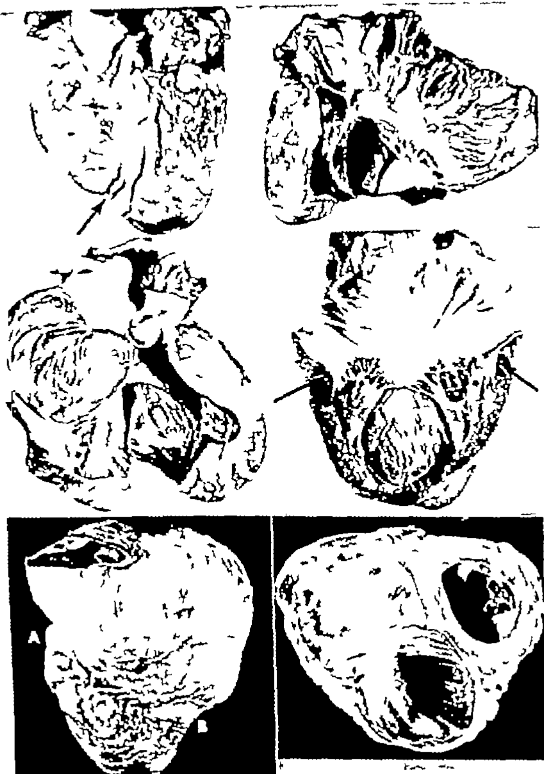


Fig. 11 For legend see opposite page.

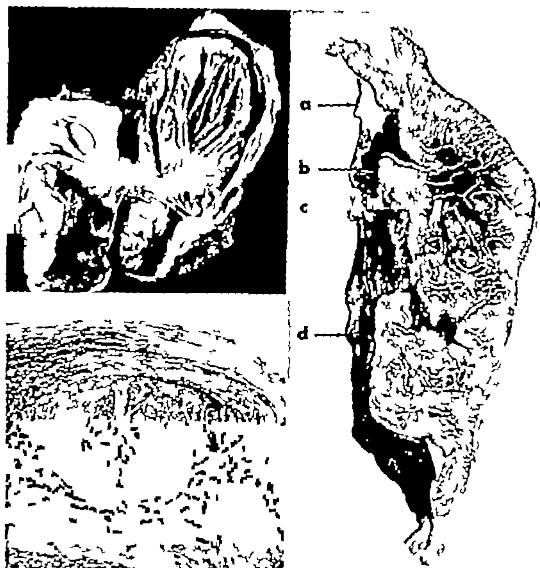


Fig. 12. Top left: This 4-year-old Rw nda hild died with advanced endocardial disease after 2 years of congestive failure. Th right ve tricle, right atrium and tremendously dilated trial appendage are shown. The endocardial scar hich is maximal t the apex is hard and measures p to 0.6 cm thick. The papillary muscles and chordae are lost in the fibrous mass. To the left there is a saccular dilatation of the outflow tract. (Heart N 15 tricuspid alve × 0.7 AFIP Neg 66-7420.)

Right: This is a full section of right ventricle. The posterior tricuspid leaflet is at ( ), and there is dense scar tissue—seen here black—on the endocardium behind it. Scar tissue has incarcerated the papillary muscle at (b). Maximum endocardial scar tissue lies between levels (c) and (d). It penetrates the myocardium to the subepicardial region at ( ). There are m ltiple foci of endocardial calcification. One is t (d). (Heart N 15 right entricle, Masson × 2.7 AFIP Neg 66-7421.)

Bottom left: This photograph shows a papillary muscle encased in endocardial scar. The scar is composed of elastica and collagen. (Heart No. 15 right ventricle Movat, × 70 AFIP Neg 66-1431.)

The cause of endomyocardial fibrosis remains unknown but the consistent mucinous swelling of the cardiac "ground substance" and vessels plus the focal nonsuppurative disintegration of collagen suggest to us that hypersensitivity is the underlying mechanism. Although rheumatic heart disease and endomyocardial fibrosis have a number of common features, including diffuse and focal disruption of the cardiac connective tissues, the consistent differences in RHD and EMF have convinced us that the two are different diseases. At the present time there is no microscopic

evidence to support the view that endomyocardial fibrosis in Uganda (Davies disease) has a similar histogenesis to cardiopathies in other parts of the world

We are gratef l to the following: Dr Chapman H Binford, Dr Aubrey Kagan and Dr Z. Feflar who encouraged this study in its early stages Professor Norman Miller who reviewed the manuscript Mr Robert T ankliff who took 2 of the pictures (Figure 4 top and middle left) and gave other aluable technical assistance Dr Don ld J Winslow who gave freely of his time and advice and to M jor Robert M McCully and Professors J G Thomson D Smit, H W Weber G. M Eddington, and the lat Professors B. J P Becker and E. Prates, who made hearts available for tudy

REFERENCES

1 Josserand, E., nd Gallavardin, L. De l asystolie progressive des jeunes sujets par myocardite subaigue primitive Arch. Gen. Med Series 9 6:513 1901
2. Roque, G., and Levy L Un cas de myocardite subaigue primitiv Arch d mal d coeur 7 10, 1914
3. Mahon, G. S. *Idiopathic hypertrophy of the heart with endocardial fibrosis*, Am. Heart J 12:608, 1936.
4. Comeau, W J Diffuse pariet l endocardial sclerosis, *Am. J Path* 15:277 1939
5. Reisinger J A and Blumental, B Myocardial degeneration wi h hypertrophy and failure of unknown cause Am. Heart J 22:811 1941
6. Smith, J J and Furth, J Fibrosis of the endocardium and m ocardium with mural thrombosis, *Arch Int Med* 71:602 1943
7 Thomas, W A Randall, R V Bland E. F and Castleman, B Endocardial fibroelastosis, New England J Med 251:327 1954
8 Evans, B. Obscure cardiopathy *Brit Heart J* 15 164 1957
9 Lynch, J B., and W tt, J Diffuse endomyocardial sclerosis, Brit Heart J 19 173 1957
10. A ld, W H R and W tson H *Fibroelastosis* of the heart in adolescence Bri Heart J 19 183, 1957
11 McKusick, V A and Cochran T H Constrictive endocarditis report of case Bull. Johns Hopkins Hosp 90:90, 1952
12. Gibbs, N M Ha orth, J C nd Readie-Short, J Endocardial fibroelastosis with generalized lymphadenopathy oedema, and rash, Brit. Heart J 19:193, 1957
13 Ishak, K. G and Tschumy W O J Endomyocardial fibrosis, Am. J Med. 32:645, 1962.
14 Faruque, A. A. *Adult endomyocardial fibrosis* in Britain, Lancet 2:331 1963
15. Black, M., and Fowler J M *Endomyocardial* fibrosis in Britain, Brit M J 1:682, 1965.
16. Davies, J N P Personal communication.
17 Pulvertaft, R. J V Personal communication.
18. Bedford, D E., and Konstam, G. L. S Heart failure of unknown aetiology in Africans, Brit. Heart J 8:236, 1946.
19 Edge J R.: Myocardial fibrosis following arsenical therapy Lancet 2:675, 1946.
20. D vies, J N P Endocardial fibrosis in Uganda, East African M J 25 10, 1948.
21 Davies, J N P P thology of Central African natives, East African Med. J 25:454, 1948
22 D vies, J N P Endomyocardial necrosis—A heart disease of obscure aetiology in Africans, Thesis (M D) University of Bristol, 1948.
23. Williams, A. W L., Ball, J D and Davies, J N P Endomyocardial fibrosis in Africa its diagnosis, distribution and nature, T Roy Soc Trop. Med & Hyg 48:290 1954
24 Ball, J D Williams, A W nd Davies, J N P Endomyocardial fibrosis, Lancet 1 1049 1954
25. D vies, J N P and Ball, J D The pathology of endomyocardial fibrosis in Uganda, Brit. Heart J 1 :337 1955.
26 D vies, J N P Some considerations regarding obscure diseases affecting the mural endocardium, Am. Heart J 59:600, 1960.
27 D vies, J N P Pathology and pathogenesis of endocardial disease, Cardiologia (Basel) 12 161 1963
28 Williams, A. W and Somers, K. The electrocardiogram endomyocardial fibrosis, Brit. Heart J 21:311 1960.
29 Somers, K. and Williams, A W The phonocardiogram in endomyocardial fibrosis, Brit. *Heart J* 22:346, 1960.
30 Shillingford, J P and Somers, K Clinical and haemodynamic patterns in endomyocardial fibrosis, Brit. Heart J 23:433, 1961
31 Gillanders, H D N tritional heart disease, Brit. Heart J 13 177 1951
32. Becker B J P Chatgidakis, C. G., and Van Lingen, B Cardiovascular collagenosis with parietal *endocardial thrombosis*, Circulation 7:345 1953
33 Gray I R Endocardial fibrosis, Brit. Heart J 13:387 1951
34 Abrahams, D G An unusual form of heart disease in West Africa, Lancet 2 111 1959
35 Abrahams, D G Endomyocardial fibrosis of he righ ventricle, Quart. J Med 31 1 1962.
36 Abrahams, D nd Brigden, W Syndrome of m tral incompetence myocarditis nd pulmonary hypertension in Nigeria, Brit. M J 2 134, 1961
37 Higginson J Gillanders, A D and Murray J G The heart in chronic mal trition, Brit. *Heart J* 14:213 1952
38 Higginson J Isaacson, C and Simson, I The pathology of cryptogenic heart disease, Arch. P h 70:497 1960
39 Chatgidakis, C B and Barlow J B *Primary mural endocardial disease* Med Proc 7:377 1961
40. Becker B J P Idiopathic mural endocardial disease *in South Africa*, Med Proc. 9 124 147 1963
41 Some *African Cardiomyopathies*, Report of a Joint Seminar of the Department of Pathology nd Medicine *of the University of the* W t w tersrand, Sou h African M J 31:854 1957
42. Davies, J N P The reactions of the endo-

cardium to disease, East Africa M J 39:5 1962.

43. Connor D H African cardiomyopathies, WHO Special Report April 1964

44. Brink A J Weber H W Endomyocardial fibrosis (EMF) of East, Central and West Africa compared with South Africa endomyocardiopathies, South African M J 40:455 1966

45. Thomson, J G Recent advances in human nutrition 1961 Little Brown & Company Boston p 389

46. Edington G M and Jackson J G. The pathology of heart muscle disease and endomyocardial fibrosis in Nigeria, J P th. & Bact. 86:333 1963

47. Parry E H O and Abrahams, D G The natural history of endomyocardial fibrosis, Quart J Med 34:383 1965

48. O Brien W Endocardial fibrosis in the Sudan, Brit M J 2:899 1954

49. Edington, G M Cardiovascular disease as a cause of death in the Gold Coast African, T Roy Soc Trop Med & Hyg 48:419 1954

50. Turner P P and Manson-Bahr R. E C Endomyocardial fibrosis in Kenya and Tanganyika Africans Brit Heart J 22 305 1960

51. Peuchot, C Latour H and Puech, P Documents anatomocliniques de fibrose endomyocardique rétractile acquise Arch d. mal. d coeur 53 1137 1960

52. Fournier P Vorun C Pauchant M and Marquet A Endocardite pariétale fibroplastique et filarose étude clinique hemodynamique et anatomique Lille Med 6:42 1961

53. Coelho, F and Pimental J C Diffuse endomyocardial fibrosis, Am J Med 35:569 1963

54. Coelho F and Pimental, J C Deux types morphologiques de fibrose endomyocardique Actualites C rd Angeiol I t 22:31 1963

55. La Broy E B Endomyocardial fibrosis Proc. Alum A M Ly 10 303 1937

56. Nagaratnam, N and Dissanayake R. V P Endomyocardial fibrosis in the Ceylonese, Brit. Heart J 21 167 1959

57. Samuel I and Ankleasria, N J Endomyocardial fibrosis in South India, Indian J P th. Bact 3 157 1960

58. Fagundes, L. A Endomyocardial fibrosis, report of three cases in Southern Brazil Rev Inst. Med. Trop. São Paulo (4) 198, 1963.

59. Andrade Z and Guimaraes, A. C Endomyocardial fibrosis in Bahia, Brazil, Brit. Heart J 26:813 1964

60. Correa, P Restrepo, C., Garcia C., and Quiroz, A. C Pathology of heart diseases of undetermined etiology which occur in Cali, Colombia, Am. Heart J 66:584 1963.

61. Yoshida, T Nimura, Y Sakakibara, H Matsutani, K Nishizaki, K. and Nakata, T A diffuse endocardial fibroelastosis with markedly dilated right atrium observed in an adult, Jap. Heart J 5:85 1964

62. Brown, J M and Burnell R. H A case of endomyocardial fibrosis, M J Aust. 1:937 1965

63. World Health Organization, Cardiomyopathies, B ll. WHO 33:257 1965

64. D Arbela, P G., and Somers, K. Endomyocardial fibrosis in Uganda, Proc III Asian-Pacific Congr Cardiologia, Kyoto, 1964 p. 120

65. Shaper A. G. Endomyocardial fibrosis and rheumatic heart disease Lancet 1:639 1966

66. Shaper A G and Coles, R M The tribal distribution of endomyocardial fibrosis in Uganda, Brit Heart J 27 121 1965

67. Special Committee report Jones criteria (modified) for guidance in the diagnosis of rheumatic fever Circulation 13:617 1956

68. Sternon, J Parmentier R Kenis, J and Vanbreuseghem R Filariose et endocardite fibroplastique à propos d un cas, Ann. Soc Belge Méd trop. 4:351 1962.

69. Ive, F A and Brockington I G Letter to the editor Endomyocardial fibrosis and filariasis, Lancet 1:212, 1966

70. Brockington, I G and Wills, A J Letter to the editor Endomyocardial fibrosis and filariasis, Lancet 1:598, 1966.

71. Somers, K et al To be published

72. Brockington, I G Personal communication.

73. Roberts W C and Sjoerdsma A The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease) Am. J Med. 36:5, 1964

74. McKinney B and Crawford, M A Fibrosis in guinea pig heart produced by plantain diet Lancet 2:880 1965.

75. Van Der Geld H Somers, K. and Peetoom F Endomyocardial fibrosis, Lancet 1:48, 1966.

76. Van Der Geld, H Peetoom F Somers K and Kanyerezi, B R Immunohistological and serological studies in endomyocardial fibrosis Lancet 1210 1966

77. Watt, J M and Breyer Brandwijk, M G The medicinal and poisonous plants of Southern and Eastern Africa, ed. 2, Edinburgh & London, 1962, E & S Livingstone Ltd p. 901

Cardiovascular stress (electrocardiographic changes) produced by driving an automobile

Ernst Simonson, M.D.
Charles Baker, M.S.
Neal Burns, Ph.D.
Charles Keiper, M.S.
O. H. Schmitt, Ph.D.
Stirling Stackhouse, Ph.D.
Minneapolis, Minn.

Driving an automobile is undoubtedly a major contributor to the general stress of life in the American population, yet very little is known about the physiological stress involved. The death rate due to automobile accidents in some age brackets is the fourth highest among all causes. Compared with the large amount of research devoted to the first three causes (heart disease, cancer, cerebrovascular accidents), the number of investigations on physiological changes associated with driving an automobile is very small. Of the limited previous research that has been done, most of these investigations have been based on the psychological characteristics or visual capabilities of the driver,[1-4] or the gross physical condition of the driver as affected by hours of continuous driving behavior. Changes of the galvanic skin responses (GSR) dependent on traffic and road conditions were studied by Michaels, Platt, and by Taylor[7] with divergent results. There seems to be some general agreement that human factors are responsible for the majority of vehicle accidents, although conclusive statistical evidence is not available.

The type of physiological stress involved in driving is probably complex, and a comprehensive study involving recording of electroencephalogram (EEG), electrocardiogram (ECG), GSR, blood pressure, respiration, and a vigilance test, together with performance of both vehicle and driver, has been initiated. It appears, even from preliminary results, that there is a significant cardiovascular involvement in the general stress of driving an automobile.

We thought that a review of the previous work on cardiovascular changes during automobile driving together with these preliminary results of our study would be of interest.

Experimental

Heart rate. The most extensive research of cardiovascular involvement in driving an automobile has been performed by Hoffmann in West Germany. The pulse rate was determined from the ECG (three Nehb leads) telemetered *to the laboratory*

From the Laboratory of Physiological Hygiene, University of Minnesota, and Mount Sinai Hospital, Minneapolis, Minn.
Supported in part by United States Public Health Service Grants NB-01839-07, AC-00113-01, and UI-00012.
Received for publication April 26, 1967.

This procedure limited the driving distance to 30 Km. Driving tended to increase the heart rate to an extent dependent on traffic conditions. The data are presented in frequency distributions of percentage of 600 healthy drivers with increase of heart rate up to 60 per cent over the resting heart rate tabulated in intervals of 10 per cent. Absolute values are not given. Low density (rural) highway driving never produced an increase of the heart rate in excess of 20 per cent, while in urban driving 28.7 per cent of drivers and in critical situation (overtaking, sudden stops, etc.) 42.3 per cent of healthy drivers had increases of heart rate above 20 per cent of the resting rate. A marked increase of 40 per cent or more of the control value occurred during city driving in 7.9 per cent and in critical situations in 14.0 per cent of the drivers.

It is of considerable interest that there was no significant effect of mere speed (up to 145 Km. per hour or 90 m.p.h.) on the heart rate, while there was some effect related to driving experience. In urban traffic, pulse rate increases of more than 40 per cent over the resting heart rate occurred in 13 of 57 drivers (24.6 per cent) with experience up to 10,000 Km., and in 16 of 256 drivers (6.2 per cent) with experience from 50,000 to 250,000 Km. There was no significant differentiation over 250,000 Km.

A total of 76 drivers with coronary disease did not appear to differ significantly in distribution of heart rate increases in the various traffic conditions, at least over the small number available for this sample.[1] In another series, Hoffmann compared the heart rate of 116 healthy male drivers and 32 drivers with "vegetative Labilität." This is a somewhat vague syndrome of overexcitability of the autonomic nervous system involving finger tremor, increased tendency to sweating, exaggerated reflexes, and exaggerated variations of heart rate and blood pressure (±15 per cent even in resting conditions), perhaps roughly comparable to patients with cardiovascular neurosis or hyperreactors. In driving "without disturbance" none of the healthy drivers had an increase of the heart rate over 20 per cent of the resting rate, while this occurred in 1 of 32 drivers with "vegetative Labilität." In critical situations, increase of heart rate exceeding 20 per cent of the resting rate occurred in 39 per cent of healthy drivers and in 75 per cent of the patients.

Dupuis[13] simultaneously recorded the pulse rate by means of telemetry and road events by means of a movie camera mounted behind the driver. Thus it was possible to relate changes of the heart rate to road events. The heart rate responded instantaneously and markedly to road events such as sudden stops, acceleration, overtaking, or dangerous curves. It is of interest that the increase started with the appearance of such critical situations and before the action of the driver (i.e., before sudden stops, etc.) and lasted only a few minutes. The increase of the pulse rate in heavy traffic volumes ranged from 15 to 30 beats per minute, and in overtaking, up to 45 beats per minute. There was a sharp initial increase of the pulse rate at the start of driving (20 to 30 beats), but then the pulse rate decreased until a level was reached typical of the given traffic situation. In confirmation of Hoffmann's findings, speed (up to 82 m.p.h.) was not a determining factor. All subjects were healthy and repeatedly investigated and thoroughly familiar with the vehicle and the testing procedure. Increase of the pulse rate also occurred in response to detours or reaction of passengers. The greatest increase of the pulse rate (by 50 beats per minute) occurred on being stopped by a police car for vehicle control.

Taggart and Gibbons[14] found in dense fast moving traffic an increase of the heart rate in the telemetered ECG of nine healthy drivers from the resting range of from 70 to 85 up to as much as 100 to 140.

In a study by Collins and associates of three drivers, the telemetered pulse rate also showed large fluctuations in response to road events, to street driving, and to freeway driving. A tendency to a decreased heart rate from an initial value of 110 at the start of driving was seen in one of the five tracings published. One subject, a 30-year-old woman, was studied as a driver and as a passenger in heavy traffic situations. The heart rate of the subject as a passenger was about 20 beats per minute higher, but the experiments

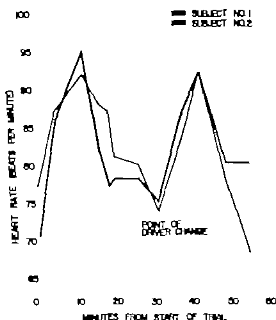


Fig. 1. Response of heart rate of driver and passenger during two consecutive periods of 30 minutes of city driving. At the vertical line, the driver and the passenger change roles. The response of the heart rate of driver and passenger is practically identical.

were done on different occasions, so that some differences in the traffic situation cannot be ruled out.

In our experiments, we recorded the heart rate of the driver and the passenger intermittently at short intervals in the *same ride; at half time, the driver and the* passenger changed roles. The results are shown in Fig. 1. The response of the driver and the passenger is nearly identical. This is not surprising since the passenger often shares with the driver the same emotional stress situation. We also found the heart rate to be a sensitive index in the response to critical road events.

In long distance driving (up to 16 hours) Suenaga, Goto and Torigoe[1] found a general tendency to a decreased pulse rate from the initial values. The decrease was less pronounced when two drivers alternated instead of one driving continuously. They believe that the decrease of the heart rate is due to fatigue, because there seemed to be some correlation with feeling sleepy. There is, however, no evidence that fatigue decreases the pulse rate, while an increase of the pulse rate with fatigue has been observed in other types of work.[15]

In another investigation[17] two drivers were compared in two cars over the same route passing through seven cities, one car driving at moderate speed (mean speed 37.7 Km. per hour, maximum speed 60 Km. per hour), the other at fast speed (mean 43.8, maximum 120 Km. per hour). The duration of the drives was 1½ and 2 hours. Large fluctuations of the pulse rate occurred, up to 40 beats per minute, dependent on road events, more so in the driver of the fast car. The average level of the pulse rate was 15 beats per minute higher at fast than at slow speed. The results appear to be contradictory to those of Hoffmann and Dupuis. However, the German investigators studied the effect of speed in highway driving, while the Japanese investigators included city driving, resulting probably in a greater number of critical situations. Suenaga and associates found that driving through a 2½ mile long tunnel (six to seven minutes) with a CO content varying from 0.002 to 0.010 per cent did not affect the pulse rate.

While we are primarily interested in the effect of ordinary city and highway driving, Collins'[7] observations on racing-car drivers are of interest because car racing may show in exaggerated degree the physiological stress involved in driving an automobile. There is a steep increase of the telemetered pulse rate with the beginning *of the race up to 170 to 200 beats per* minute or even more. It either maintains that level or drops slightly during the race with comparatively small fluctuations followed by a precipitous drop after the race. These findings were corroborated by Taggart and Gibbons[13] who found in three drivers during competitive circuit racing an increase of the heart rate between 190 and 205. The drivers were unaware of palpitation or any other symptoms. In all investigations with the heart rate determined from the ECG, the increase of heart rate was due to sinus tachycardia.

Blood pressure. In 600 healthy drivers, the blood pressure showed a tendency to increase with traffic density, but even in critical situations, it exceeded 20 per cent of the resting value in only 1.2 per cent of

the drivers. There was no change in 57.3 per cent and in 8 6 per cent of the drivers the increase was between 0 and 10 per cent of the resting value. There was again no effects of speeds up to 145 Km per hour (90 m p h) In healthy drivers, therefore the blood pressure is considerably less responsive to the stress of driving than the pulse rate The situation is different in cardiovascular patients. Only 25 per cent of 32 drivers with vegetative Labilitat (hyperreactors) showed no changes of blood pressure in critical situations, and in 50 per cent the increase of blood pressure did not exceed 10 per cent of its resting value In five drivers (15 6 per cent) the increase exceeded 20 per cent. In some individual patients a pronounced blood pressure increase occurred for instance in a male driver 31 years of age without symptoms of circulatory insufficiency the blood pressure increased during city driving (25 minutes) from 125 80 to 1 0 100 mm Hg

In 6 drivers with coronary artery disease the blood pressure always increased in critical situations exceeding 20 per cent of the resting value in 11 5 per cent. There was as in the normal groups a tendency to greater increase with traffic density

Tilting test In order to evaluate cardiovascular effects of automobile racing the tilting test (0 degrees five minutes duration) was performed after the race in several racing-car drivers. Controls before the race were not performed however in all subjects and the number of experiments in the individual drivers varied from one to five Four types of response were differentiated (1) decrease in both systolic and diastolic pressure (2) decrease in systolic and increase in diastolic pressure—which was the most common response, (3) increase of both systolic and diastolic pressure and (4) moderate or marked decrease in pulse pressure Obviously responses 2 and 4 are similar in type.

Due to the varying number of repeats the same driver may appear (on different occasions) in all of these four categories. Thus statistical evaluation of the results is difficult, but it appears that the unfavorable responses 1 and 4 occur quite frequently There was no relationship of the response to tilting to age or apparent physical condition.

Electrocardiogram (ECG) Hoffmann[41] investigated ECG changes by means of telemetered ECGs (Nehb leads) in 600 healthy male drivers, 26 ambulatory drivers with coronary heart disease and 32 drivers with vegetative Labilitat (hyperreactors) (the Nehb leads were quite commonly used in Germany during the forties, but are now practically abandoned) The changes of the ECG were presented in terms of presence or absence of pathological changes. The criteria for these abnormal changes are not given which is unfortunate because of the large observer variation in the subjective interpretation of the ECG[39] While details of changes which were considered as abnormal were not given depression of the S-T segment and inversion of the T wave were among the pathological changes as shown by illustrations. With these reservations, there appears to be a highly significant difference between healthy drivers and patients with coronary heart disease. In highway driving with low traffic density no pathological changes were observed in healthy drivers, as compared to 11 5 per cent in drivers with coronary heart disease In city driving pathological changes occurred in 16 per cent of healthy drivers and 46 per cent of drivers with coronary insufficiency There was also a higher percentage of pathological changes of the ECG in hyperreactive drivers than in healthy drivers.[1]

In critical situations, abnormal ECG changes occurred in 21 of 32 hyperreactive drivers (65 5 per cent) and in 16 of 26 drivers with ambulatory coronary artery disease (53 8 per cent) The changes of the S-T segment and the T wave were assumed to be due to myocardial hypoxia, resulting from either increased myocardial oxygen consumption or coronary spasm Thus the changes of heart rate blood pressure and ECG were significantly more pronounced in hyperreactors and patients with coronary artery disease. It may be implied that driving a car is a greater stress for cardiovascular patients.

ST depression with flattening of the T wave or with diphasic T waves was seen in two of nine healthy drivers in dense traffic (London Trafalgar Square) A

telemetered bipolar left ventricular lead was used probably similar to that used in our study but the exact electrode location was not given. These changes occurred both in exercise and during anxiety situations while driving.[*] Intravenous injection of 1.2 mg. of atropine in those two subjects produced a degree of tachycardia similar to that occurring during driving but without ST-T changes. The authors conclude that the tachycardia per se was not responsible for the ST-T depression.

Heart attacks during driving. The first report of death due to coronary occlusion occurring during driving goes back to Le Count and Rukstinat.[11] No accident was involved in the three cases. Buchaly[12] found one case of autopsy-confirmed coronary occlusion during driving in a 40-year-old man.

Sudden cardiac death during driving with or without traffic accident was also reported by Smith and Friedman[13] and Schwarz. The Essen Institute for Safety in Mining and Traffic collected a material of 104 cases with sudden death during driving. Traffic accidents resulted in only a small minority (quoted from Hoffmann).[16] Of 60 drivers who succumbed to sudden cardiac death in 11 the fatal attack occurred during driving which appears to be a rather high incidence. Levy[14] reports the case of a bus driver with autopsy-confirmed coronary occlusion which occurred during driving. The bus crashed into the East River (New York) and six passengers died in addition to the driver.

Looking through the material of the large University Hospital in Bonn, Hoffmann[16] found 31 cases of nonfatal myocardial infarction hospitalized during a period of ten years where the attack occurred during driving. Traffic accidents (mostly minor) were involved in ten cases. The total number of patients hospitalized with myocardial infarction over the ten-year period was not given but these 31 cases must represent a very small fraction of the total.

Hoffmann concluded that the stress of driving may produce a myocardial infarction in persons with existing coronary atherosclerosis which would be according to large autopsy material[17] the majority of the North American population. The prevalence of coronary artery disease is similar in Western Europe. However, Hoffmann relies in this conclusion more on his experimental results than on statistical material. There is actually no reliable statistical material available to answer this important question. Unless heart attacks involve an accident, there is no record or only very exceptionally. In 1965 there were 11 cases of death during driving reported in the state of Minnesota which did not involve road accidents. The majority were heart attacks (coroner's report).[18] Not all heart attacks during driving are fatal; in fact, probably only a small minority. In many accidents, illness is not reported even when present. Out of 82,000 reported automobile accidents in Minnesota during 1966 involving 140,000 drivers, only in 159 cases was illness reported as a contributory cause.[19]

There are about 575,000 male and 425,000 female licensed drivers over 40 years of age in the state of Minnesota (1966). From several longitudinal studies[20-22] it may be expected that about 0.7 per cent of the male population over 40 years of age originally screened as to absence of clinically detectable disease will have myocardial infarction per year and an additional 0.3 per cent will develop serious coronary insufficiency amounting to about 1 per cent together. The percentage will be *higher* in the average unscreened population, perhaps tentatively 1.5 per cent. The information is concerned with the number of patients and not the number of attacks, which will be appreciably higher. No precise information on the number of attacks (myocardial infarction or angina) is available, but for a crude estimate, 2.5 per cent may be permissible, amounting to 14,375 heart attacks for Minnesota male drivers over 40 years. Based on data by Staffeld and Oster[23] we conservatively estimate that men over 40 years of age spend one hour per day driving automobiles. Assuming nearly *random* distribution of heart attacks during the day

*Bellet, [illegible] J.S.M. [illegible] 200: 33-34, 1967) recently found ST-T depressions during [illegible] 30 minute [illegible] drive in eight of 44 patients with coronary heart disease, in confirmation of Hoffmann's findings, but failed to find changes in healthy drivers as observed by Hoffmann, Taggart and Gibbons, and in our experiments.

(actually slightly higher) at least 4 per cent of the heart attacks and probably closer to 5 per cent should occur during driving. This would mean that approximately 700 heart attacks may be expected to occur in the male Minnesota drivers over 40 years within one year. The expected number of heart attacks in female drivers is substantially smaller, but a total of 1,000 heart attacks may be expected to occur during driving in Minnesota, assuming that driving as such does not promote heart attacks. Some heart attacks will occur also in drivers below 40 years. The number of 1,000 and probably more heart attacks during driving is substantial as a potential accident risk.

According to a recent survey by Tavia and associates[20] of 14,621,000 adults from 18 to 9 years of noninstitutional United States population, 2.8 per cent have definite and per cent have suspected coronary artery disease. This is a higher prevalence of coronary artery disease than found in other samples, and on this basis a substantially higher number of heart attacks may be expected.

In view of this situation it is not surprising that heart attacks during driving have been reported in the literature; the surprising fact is that there have been so few.

Exploratory experiment. Exploratory experiments were performed in order to obtain some information about repeat variation of electrocardiographic changes in driving over the same route in one healthy subject (S) and changes of the ECG in driving over long distances (from 00 to 00 miles of nearly continuous driving without sleep). Data were obtained for a total of over 6,000 miles of driving. There does not seem to be any information about ECG changes in long distance driving. It may be assumed that, as in any other physiological stress situation, accumulation of stress occurs during prolonged activity.

Subjects. Five male subjects were used: A (26 years), B (40 years), C (77 years), and S (34 years) were clinically healthy. D (32 years) has had nephrosis with chronic albuminuria for several years with otherwise negative clinical findings. His working capacity is not impaired (estimated 65 working hours per week). C has the largest driving experience of the five subjects. The resting conventional 12 lead ECG as well as the exercise test (ten minutes walking on the treadmill at a speed of 3 m.p.h. and 5 per cent grade) of all five subjects was within normal limits.

Procedure, equipment. The ECG was taken with a bipolar lead (manubrium-C5 position) in intervals of approximately 20 minutes with A, B, C, and D. The start of each driving session was preceded by a resting ECG in the same position. This lead was shown in a comparison of 22 leads to combine high sensitivity to detect S-T and T changes with little interference from movements.[21] In all records obtained the signal-to-noise ratio was large enough for quantitative analysis of T wave changes, and in many records the noise was negligible. This lead is similar in pattern to conventional Lead V_4.

The ECG on D's trip (Minneapolis to New York) was recorded with the battery-operated Honeywell Cardioview and on the other trips with a portable Sanborn electrocardiograph Model 500 and an inverter. The use of Beckman electrodes was most satisfactory; no electrode slippage occurred during any of the trips. The electrodes would stay in place for 48 hours. A logbook was kept of driving events and conditions.

An experimental car (1965 Ford Country Squire Station Wagon) equipped with power steering and brakes, automatic transmission, and air conditioning was used for the driving experiments with A, B, C, and S. Comfortable temperature was maintained by an air conditioner. D used his personal car (1962 Buick Electra).

The total distances driven are shown in Table I.

Table I

Subject	Miles driven	Duration (days)
C	200	1
S	300	1
B	870	2
D	2,300	4
A	2,600	4

Results

The heart rate was noted to respond distinctly to critical situations such as overtaking a car sudden stops, and such in confirmation with the observations of Hoffmann Dupuis,[12] and Collins and associates.[13]

Repeat variation was investigated in subject S in eight drives from home to office and back during the rush hour involving suburban and urban driving for a duration of 30 minutes. Of course, none of the drives was exactly identical but the number of events, speed etc. was fairly well averaged. Fig 2 shows a representative selection of ECG records. There is a distinct lowering or flattening of the T wave quite similar on the different days. Therefore the results are fairly well reproducible.

Results of long distance driving are shown in Figs. 3 and 4. In C the T wave decreased after four hours of driving to half its original size (Fig 3) In A transient flattening of the previously positive T wave developed after four hours of driving with some correlation to road events (Fig 3) and in B transient inversion developed after one hour (Fig 4) As driving continued the periods of T wave flattening in A or inversion in B became more frequent and more prolonged After interruption of driving the T wave recovered to approximately two thirds its original size but became flat or inverted shortly after resumption of driving In S the lowering of the T wave in the drive over 300 miles was similar to that noted in shorter drives during the rush hour (Fig 7)

Discussion

It appears that significant ECG changes may occur in healthy subjects during short drives as well as long distance driving Although it would be premature to generalize it may be inferred that there is a significant myocardial involvement in the stress of driving an automobile, even in some apparently healthy drivers.

It is unlikely that the ECG changes during driving are due to myocardial ischemia. The oxygen consumption has, to the best of our knowledge, never been measured systematically during driving of an automobile, but is probably in the order of 5 ml per kilogram per minute, estimated from occupations with a similar degree of exertion[16] By comparison the mean oxygen consumption of ten normal subjects for Master's double two-step

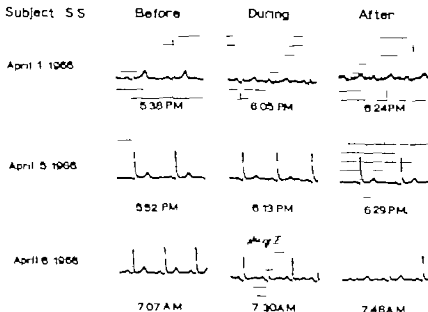


Fig 2. ECG changes (lowering of T waves) during suburban-urban driving of about 30 minutes. The changes on three different occasions representative for eight drives, are similar demonstrating reproducibility

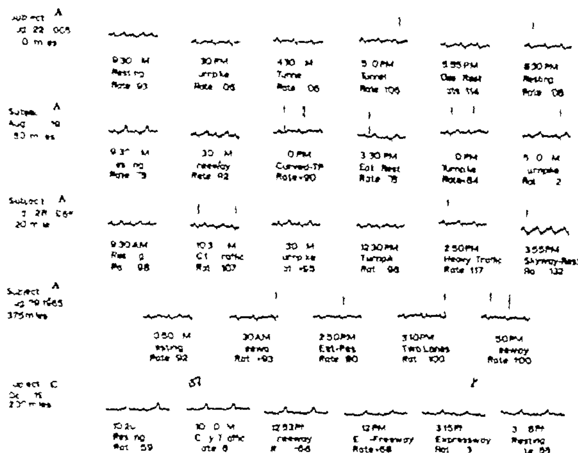


Fig. 3 Change of the bipolar (manubrium C5) ECG before and during driving an automobile. The resting records (first) are taken in driving position. Flattening of the T ... some partial ... situation Aug 2 at 4 30 P.M. and 5 10 ... passing through the tunnel Aug 25 ... 1 10 P.M. ... turnpike Aug 28 2 50 ... heavy traffic prolonged flattening of T ... of driving from 11 30 ... 4 50 ... interrupted by partial recovery during rest for meal (2 50 ...). C shows decrease of T amplitude with length of driving

test was 23 5 ml per minute per kilogram of body weight[36] which is nearly identical to the oxygen consumption in walking on the treadmill at a speed of 3 5 m p h 5 per cent grade[37] As mentioned before the exercise test (walking on the treadmill at 3 5 m p h 5 per cent grade) was normal in all five subjects. Conventional ECG leads were taken in supine position before and 1 6 and 10 minutes after exercise the bipolar manubrium C5 lead was taken by means of telemetry before exercise in supine and in standing position during the first second and third minutes of exercise and seated ten seconds after exercise. No significant S-T depression or T inversion occurred during or after exercise

Intake of a moderate meal (1 260 calories) produces a decrease of positive T waves in healthy men and women but no inversion In spite of very substantial and statistically very significant changes in the various ECG items, the postmeal ECGs all remained within the normal limits[35]

The electrocardiographic changes during driving occurred before as well as after food intake and are not more pronounced after food than before eating The partial recovery of T wave changes during interruptions of driving is also independent of meal intake The ECG changes during driving therefore are not related to meal intake

Most likely the changes of the ECG

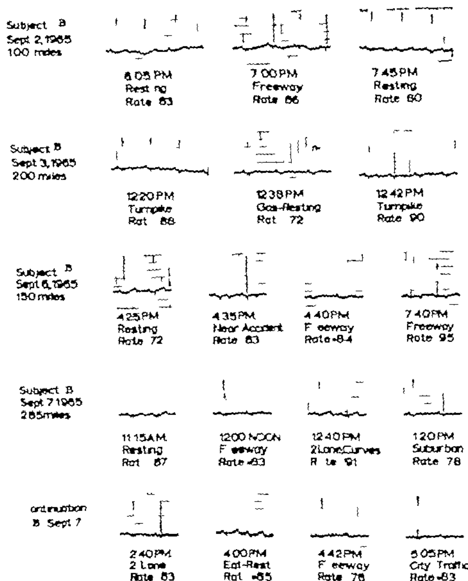


Fig 4 Subject B Transient in ersion of the T ave, with some correlation to stressf l situa ions and partial recovery during rest (ith or w thout meal intake)

during driving are due to emotional stress mediated through the autonomic nervous system and hormonal system particularly the ad enal system There is a large elec trocardiographic literature in part re viewed by Simonson[38] on changes of the S-T segment and T wave invers on in subjects during anxiety producing psycho-logical tests and interviews. Significant neurogenic ECG changes have been found n animal experimentation and n patients.[31] It is of interest that no gross a rhythmias were observed during driving. The results show that significant ECG changes may occur during driving and often to a degree which would be an abnormal response in other stress situatsons su h as exercise or hypoxia test. There is, therefore a sig nificant cardiovascular involvement in ordi nary driving which cannot be ignored in the analysis of the over all physiological stress situation

Summary

A review of cardiovascular changes during driving an automobile s presented.

The heart rate responds instantaneously to critical situations and in stressful situations such as car racing increases rapidly to frequencies of 200 per minute or more. Blood pressure is less responsive. Significant ST depression and T wave changes were reported in healthy drivers and more so in ambulatory patients with coronary heart disease or in hyperreactors.

In the experimental part significant changes of the T wave in the ECG are reported which occurred in five men (having normal resting and postexercise ECG's) while driving an automobile over distances of 200 to 1,600 miles. The previously positive T wave of a bipolar manubrium-C5 lead similar in pattern of V_4 decreased to half its original size in one subject after three hours of driving. Transient flattening or inversion of the T wave developed in two other subjects after one to four hours of driving with some correlation to road events. The changes recovered partially during rest periods. The repeatability of ECG changes in eight drives over the same route (suburban and urban driving during rush hour) was quite good.

We wish to thank Mr. Fletcher N. Platt, Manager, Traffic Safety Department, Ford Motor Company, for arranging the loan of the car used for these experiments.

REFERENCES

1. Bloomer, R. H.: Perceptual defense and vigilance and driving safety, Traffic Quart. 16:549, 1962.
2. Fine, B. J.: Introversion-extraversion and motor vehicle driver behavior, Perceptual Motor Skill 16:95, 1963.
3. Sherman, R. A.: Seeing habits and vision: A neglected area in traffic safety, Traffic Quart. 15:607, 1961.
4. Platt, F. N.: Operations analysis of traffic safety, International Road Safety and Traffic Review 6:1, 1959.
5. Michael, R. M.: Effect of expressway design on driver tension responses, Pub. Road 32:107, 196_.
6. Platt, F. N.: Personal communication.
7. Taylor, D. H.: Driver galvanic skin response and the risk of accident, Ergonomics 7:439, 1964.
8. Hoffmann, H.: Medizinisch-psychologische Untersuchungen zum Fahren im Verkehrsfluss, Ztschr. f. Verk. hrssicherh. 11:145, 1965.
9. Hoffmann, H., and Reygers, W.: Kreislaufuntersuchungen bei Kraftfahrzeugfahrern unter arteriellen Fahrbedingungen, Zentralbl. f. Verkehrsmed. 3:131, 1960.
10. Hoffmann, H.: Herzkranke am Steuer von Kraftfahrzeugen, München. med. Wchnschr. 105:1790, 1963.
11. Hoffmann, H.: Experimentelle Kreislaufuntersuchungen bei gesunden und vegetativ labilen Kraftfahrzeugfahrern, Heft z. Unfallheilk. 71:127, 1962.
12. Dupuis, H.: Fortlaufende Pulsfrequenz schreibung bei Kraftfahrern und ihre Interpretation, Proc. II Kong. J. ges. h. Arbeitsmed. Suppl. 3, 1965, p. 78.
12a. Taggart, P., and Gibbons, D.: Motor car driving and the heart rate, Brit. M. J. 1:411, 1967.
13. Collins, V. P., West, W. D., McTaggart, W. G., and Maxwell, A. R.: Telemetry in driving safety study, Proc. Nat. Telemet. Conf. 1965, p. 241.
14. Suenaga, K., Goto, K., and Torigoe, M.: A study on physical changes, especially in the heart rate from the view point of accident prevention, Jap. Traffic Sc. Committee Rep. Nov. 18, 1964, p. 24.
15. Schmidtke, H.: Die Ermüdung, Stuttgart, 1965, p. 338.
16. Simonson, E.: Der heutige Stand der Theorie der Ermüdung, Erg. Physiol. 37:299, 1935.
17. Suenaga, K., Goto, K., Torigoe, H., Tamashita, Y., and Hattori, Y.: The effect on cardiac functions of the driver of speedy driving on ordinary public road, J. Kurume M. J. 28:1091, 1965.
18. Suenaga, K., Goto, K., Torigoe, H., Yamashita, Y., and Hattori, Y.: Mental and physical response of driver on passing through "Kan-Mon Tunnel" overcrowded with cars, J. Kurume M. J. 28:1096, 1965.
19. Collins, V. P.: Physiologic observation on race car drivers, NASA Report N-G-730, Washington, D. C., September 1966, p. 114.
20. Simonson, E.: Differentiation between normal and abnormal in electrocardiography, St. Louis, 1961, The C. V. Mosby Company, p. 328.
21. LeCount, E. R., and Rukstinat, G. J.: Sudden death from heart disease while motoring, J. A. M. A. 92:1347, 1929.
22. Buchaly von, J. F.: Plötzlicher Tod eines scheinbar gesunden Autofahrers, München. med. Wchnschr. No. 4, Jan. 22, 1932.
23. Smith, E., and Friedman: Second Conf. NAS-NRS Committee on Highway Safety Research 2:11, 1954.
24. Schwarz, F.: Ztschr. Verkehrssicherh. 2:205, 1954.
25. Hoffmann, H.: Der Herzinfarkt am Steuer, München. med. Wchnschr. 105:1, 1963.
26. Levy, R. L.: Heart disease in driver of public motor vehicles as a cause of accidents, J. A. M. A. 184:481-485, 1963.
27. Clawson, B. J.: Incidence of types of heart disease among 30,265 autopsies with special reference to age and sex, Am. Heart J. 22:607, 1941.
28. Staffeld, P., and Oster, G.: Personal communication, 1967.
29. Chapman, J. M., and Massey, F. J.: The interrelationship of serum cholesterol, hypertension, body weight and risk of coronary disease. Re-

sults of the first ten years follow-up in the Los Angeles heart study J Chron. Dis 17:933, 1964

30. Doyle, J T Dawber T R Kannel, W B. Kinch, S. H Kahn M S and Kahn, H. A. The relationship of cigarette smoking t coronary heart disease. The second report of the combined experience of the Albany N Y and Framingham, Mass., studies, J.A M A. 190:886, 1964
31. Lawrence, H E Carver S., Benjamin, B Christenson, W N and Strone, B. W Studies in ecology of coronary heart disease, Arch. Envir Health 9 14 1964.
32. Shapiro, S Weinblatt, E., F ank, C W and Sager R V The H I P study of incidence nd prognosis of coronary heart disease. Preliminary findings on incidence of myocardial infarction and angina, J Chron Dis. 18:527 1965
33. T vla, G M Dowell, A J and W terhouse A M Defining the prevalence of heart disease an examination survey Am. J Pub. Health 55:879 1965
34. Blackburn, H A systematic comparison of ECG chest leads commonly used in mon toring during ork, Karvonen, M and Keys, A editors Physical activity and the heart, Charles C Thomas, Publisher Springfield, Ill I press.
35. Lehmann, G. Praktische Arbeitsphysiologie St ttgart, 1962 Thieme Verlag, p. 145
36. Rowell, L B., T ylor H L Simonson, E and Carlson, W S The physiologic fallacy of ad justing for body weight in performance of the Master t o-step test, Am HEART J 70:461 1965
37. Erickson, L., Simonson, E T ylor H L Alexander H., and Keys, A. The energy cost of horizontal nd grade walking on the motor driven treadmill, Am. J Physiol 145:391 1946.
38. Simonson, E., and Keys, A The effect of an ordinary meal on the electrocardiogram. Normal standards in middle-aged men and omen, Circulation I 1000, 1950
39. Yanowitz, F Preston, J B., and Abildskov J A F nctional distribution of right and left stellat innervation t the ventricles, Circulation Res. 18:416, 1966.

The treatment of cardiogenic shock

Part IV. The use of phenoxybenzamine and chlorpromazine

*Ronald H. Dietzman, M.D.**
*Richard C. Lillehei, M.D., Ph.D.***
Minneapolis, Minn.

The response to myocardial damage is increased peripheral vasoconstriction and reduced tissue perfusion triggered by a fall in cardiac output and a consequent fall in blood pressure. This relationship is expressed by: $P = F \times R$, where P represents blood pressure, F flow or cardiac output, and R total peripheral resistance. This reflex response to low arterial pressure is mediated through stimulation of the carotid and aortic baroreceptors, which results in the outpouring of the catecholamines (epinephrine and norepinephrine) from the adrenal medulla and sympathetic nerve endings. The increase in circulating and tissue levels of catecholamines causes vasoconstriction in the adrenergically sensitive splanchnic, pulmonary, and cutaneous beds—thus the classical clinical signs of pale, cold, moist skin and reduced urinary output. This redistribution of blood flow allows for preferential perfusion of the heart and brain, Nature's way of preserving life. Yet, if we mimic Nature's response by adding to this vasoconstrictive response, we do not improve survival, because the damaged heart must work against a higher resistance, which may contribute to earlier cardiac failure. Moreover, the reduced renal blood flow may go on to anuria and renal shutdown. This change in peripheral resistance alters the myocardial work pattern. Both experimental and clinical studies have shown that cardiac work ($W = P \times F$) is reduced approximately 50 per cent during cardiogenic shock. However, under these conditions, the pressure component of work is elevated and the volume or flow component reduced. The pressure component is elevated because of the elevated peripheral resistance, and under these circumstances, myocardial oxygen consumption is increased and myocardial efficiency reduced. Thus, the peripheral vasoconstriction and increased peripheral resistance adds further injury.

Laboratory and clinical studies now indicate that treatment directed at an equitable redistribution of blood flow to *all* tissues improves survival, and this must be accomplished by reduction of vasoconstriction. With such a reduction, however, there is an increase in capacitance of the vascular system which may require additional volumes of fluid even in cardiogenic shock in order to insure an adequate venous return.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn. 55455.
Supported by the United States Public Health Service Grant [illegible].
Received for publication Sept. 11, [illegible].
*Sterling Winthrop Research Fellow.
**Professor of Surgery.

There are drugs which can reduce vasoconstriction. Two of the most promising are phenoxybenzamine and chlorpromazine. These drugs act by blocking the effects of the catecholamines on the α-receptors of the pre- and postcapillary arterioles and venules of the skin and viscera. These receptors have not been located anatomically but their presence has been functionally demonstrated. As a result of α-receptor blockade blood flow to the skin and viscera is improved and the pressure work of the heart is lessened.

The effectiveness of these drugs in the treatment of cardiogenic shock can be demonstrated in the experimental laboratory as follows. After the production of myocardial infarction in the dog by intracoronary artery microsphere embolization, there is a reduction in the cardiac output and blood pressure and a consequent rise in total peripheral resistance. This increase in total peripheral resistance reflects the magnitude of vasoconstriction. Concomitantly increased circulating levels of both epinephrine and particularly norepinephrine have been found. This vasoconstriction results in reduced tissue perfusion as can be seen by the reductions in superior mesenteric and renal artery blood flows. This fall in renal blood flow is associated with a fall in urine output. Myocardial blood flow is not reduced to the same extent but during shock the myocardium receives a greater percentage (3 to 5 times) of the cardiac output than prior to shock. With persistence of the vasoconstriction anaerobic metabolism in the affected areas increases and serum lactic acid rises. To compensate for this acidosis, the dog hyperventilates and the pCO_2 falls. When this compensation fails, serum pH falls and the dog develops a more severe acidosis and dies. The majority die within the first 24 hours, with only 25 per cent surviving longer than three days. By adding either intravenous phenoxybenzamine or chlorpromazine in a dose of 1 mg. per kilogram the entire hemodynamic picture is changed and survival is improved. The blockade of the effects of the catecholamines at the vasoconstricting α-receptor sites results in an equitable redistribution of blood flow to all regions. The total peripheral resistance falls and the tissues are perfused at a lower perfusion pressure but flow is increased and the pressure component of cardiac work is reduced—an important aspect when the myocardium is damaged. Venous return to the right atrium is maintained during such treatment by careful monitoring of right atrial pressure and the addition of volume expanders, such as plasma or low molecular weight dextran, as this pressure falls. The improved renal blood flow, for example, is mirrored by the improvement in urine output. Anaerobic metabolism is now replaced by aerobic metabolism and the serum lactic acid falls. With the stimulus to hyperventilation gone, a normal respiratory pattern ensues and the pCO_2 and pH return to the normal range. With this treatment, the survival rate in dogs with myocardial infarctions increases to over 60 per cent, a significant achievement.

Clinically, the same pattern of events occurs in cardiogenic shock after myocardial infarction or following open-heart surgery. The vasoconstriction is indicated by the pale, cold, clammy extremities, and the urine output below 25 ml. per hour. Hemodynamic measurements of these patients confirm the presence of reduced cardiac output and an elevated total pe-

Fig. 1. Course of a patient in cardiogenic shock.

ripheral resistance Elevations in both epinephrine and most notably norepinephrine also occur The resulting lactic acidosis is compensated for in man by a reduction in the pCO through hyperventilation. We have seen this same pattern of events repeatedly in patients suffering cardiogenic shock who have been monitored in detail Fig 1 depicts the course of a 41 year-old woman in cardiogenic shock after replacement of both the mitral and tricuspid valves for rheumatic valvulitis. After treatment with phenoxybenzamine (1 mg per kilogram) and maintenance of the central venous pressure at 10 mm Hg with blood and low molecular weight dextran to assure adequate venous return the signs of vasoconstriction relented The cardiac output rose and the total peripheral resistance fell to within normal limits. The skin of the extremities again became warm and pink and the urine output returned The patient recovered and is doing well one year after surgery

Phenoxybenzamine is still an experimental drug and not commercially available *for intravenous use* but the drug emphasizes the value of vasodilatation through α-receptor blockade coupled with adequate volume replacement in the treatment of cardiogenic shock The hazard of this and similar acting drugs is the dramatic increase in vascular capacity which results from their use Hence these drugs must not be used unless the physician is willing to assess central venous or right atrial pressure at the same time Phenoxybenzamine is usually given intravenously in a dose of 1 mg per kilogram diluted in 100 ml of 5 per cent dextrose in water dripped in over a 2 to 4 hour period The central venous pressure is maintained at 10 to 12 cm H_2O before during and for 24 hours after its administration The choice of the volume expander depends upon the hematocrit If the hematocrit is within the normal range either plasma or low molecular weight dextran is given Dextran has the advantage of being hypertonic and also acts as an osmotic diuretic which further improves urine output

Chlorpromazine is commercially available and the same admonition outlined for phenoxybenzamine must be heeded The one important exception is that the drug may be given more rapidly over a 10 to 15 minute period of time. Chlorpromazine does not produce the dramatic increases in vascular capacitance seen with phenoxybenzamine because its α-blocking effects are not nearly as strong but the same caution must obtain in providing volume replacement if indicated by decrease in central venous or right atrial pressure

In summary cardiogenic shock is associated with a fall in blood pressure secondary to a fall in cardiac output The associated vasoconstriction although initially lifesaving subsequently leads to death if allowed to continue unchecked Reduction of this vasoconstrictive response with the α adrenergic blocking drugs, phenoxybenzamine or chlorpromazine has been found by us to be lifesaving

REFERENCES

1. Winnie A P and Collins V J Pharmacologic adjuncts to the management of shock, Clin Anesth. 2:59 1965
2. Bloch J H Pierce C H and Lillehei, R C Adrenergic blocking agents in the treatment of shock Ann Rev Med. 17:483, 1966.
3. Dietzman, R H Bloch J H Feemster J A Idezuki, Y and Lillehei R C Mechanisms in the production of shock, Surgery 62:645 1967
4. Dietzman, R. H Feemster J A Idezuki, Y Bloch, J H and Lillehei, R. L. Peripheral resistance changes during shock in man, Angiology 1967 in press.

A clinical study on the mechanism of the antiarrhythmic action of a new antagonist to β-adrenergic receptor

Animal studies of the antiarrhythmic effects of pronethalol and propranolol indicate that these agents may influence cardiac rhythm through two different mechanisms of action. First, the agents can abolish catecholamine-induced arrhythmias through blockade of the β-adrenergic receptor. Second, they influence the myocardial-cell membrane more directly, like quinidine or local anesthetic agents. At present there is no information available about the relative importance of these two mechanisms of action.

H 56/28 (1-(o-allylphenoxy)-3-isopropylamino-2-propanol hydrochloride) is a new β-adrenergic receptor[1] antagonist which, in animal studies, has been found to counteract arrhythmias through the same two mechanisms as pronethalol and propranolol.

The β-receptor-antagonistic activity of H 56/28 was found to be equal to that of propranolol in both man and animals. The evidence that H 56/28 has an antiarrhythmic action through mechanisms other than β-receptor blockade is (just as for pronethalol and propranolol) predominantly based on animal studies with its optical isomers. The dextro isomer of H 56/28 has about one hundredth of the activity of the levo isomer in blocking β-receptor stimuli. However, ouabain-induced ventricular tachycardia in dogs was cleared at least as effectively by H 56/28 dextro as by H 56/28 levo or racemic propranolol. In isolated papillary muscle racemic H 56/28 and its two isomers were approximately equally effective in prolonging the refractory period and increasing the stimulation threshold. The two isomers of H 56/28 had approximately equal local-anesthetic activity. These studies indicate that, in comparison to racemic H 56/28, the dextro isomer has little β-receptor-blocking activity but approximately equal direct action on the myocardial-cell membrane.

We will here give a brief report of a study with the racemic and the dextro forms of H 56/28 in patients with cardiac arrhythmias.

Racemic H 56/28 was administered intravenously in doses of from 4 to 20 mg (mean dose, 13 mg) to 43 patients with a variety of mainly acute arrhythmias. The series included 14 patients with acute myocardial infarction, 11 with chronic coronary heart disease, and 7 with valvular heart disease.

The results, reported in detail elsewhere, can be summarized as follows. Racemic H 56/28 consistently reduced heart rate in sinus tachycardia (10 patients), diminished rapid ventricular rate in atrial fibrillation (8 patients), completely suppressed arrhythmia in 11 of 13 patients with multiple ventricular ectopic beats and/or bigeminy, and abolished arrhythmias occurring after electroconversion of atrial fibrillation (4 patients). In 3 patients with paroxysmal supraventricular tachycardia and in one of 4 patients with paroxysmal ventricular tachycardia, the injection of racemic H 56/28 was followed by conversion to normal sinus rhythm. In practically all patients on whom H 56/28 had positive effect, the antiarrhythmic action occurred during the injection of the drug and persisted for the whole observation period of 90 minutes.

One patient with supraventricular tachycardia sustained reversible circulatory collapse immediately after the injection of racemic H 56/28. In one patient with severe myocardial infarction and ventricular tachycardia, H 56/28 markedly reduced the blood pressure. In one patient with partial AV block, H 56/28 produced complete AV dissociation. Otherwise, no significant side effects were observed.

The results indicate that racemic H 56/28 can reduce rapid impulse production in the sinus node, depress ectopic impulse foci in atria and ventricles, and depress AV conduction—i.e., actions similar to those previously reported for racemic pronethalol and propranolol.

On the basis of the animal data referred to above, an investigation of the clinical antiarrhythmic effect of the dextro isomer of H 56/28 was initiated to clarify the mechanism of the antiarrhythmic action of racemic H 56/28. The dextro isomer of H 56/28 was administered intravenously in doses of from 5 to 20 mg (mean dose, 18 mg) to 14 patients with acute arrhythmias of essentially the same types as in the above study with racemic H 56/28. The series included 2 patients with sinus tachycardia, 2 patients with atrial fibrillation, 1 patient with atrial flutter, 7 patients with multiple ventricular ectopic beats, and 2 patients with paroxysmal supraventricular tachycardia.

The injection of the dextro isomer of H 56/28 did not influence the arrhythmias in any of these patients, nor were any side effects observed after the injection.

In view of this negative result and the related animal data, it can be concluded that the clinical antiarrhythmic effect of racemic H 56/28 reported

Umeå, A. Hässle, Göteborg, Sweden.

bove were totally or predominantly due to its β-adrenergic-receptor blocking property

E. Link M.D.
R. Ruosteenoja M.D.
L. Siitonen M.D.
First Medical Clinic
Central Hospital
Tampere Finland

REFERENCES

1. Epstein, S. E. and Braunwald, E. Beta-adrenergic receptor blocking drugs. Mechanism of action and clinical application, New England J. Med. 17 1106, 1966
2. Brändström, A. Corrodi, H. Junggren, U. and Jonsson T. E. Synthesis of some β-adrenergic blocking agents, Acta pharmaceut. sued 3:303, 1966
3. Dore B. R. Garberg L. and Johansson, B. The effect of propranolol and the dextro and laevo isomers of H 56/28 upon ouabain-induced ventricular tachycardia in unanaesthetized dogs, Acta pharmacol. et toxicol. 25 suppl. 2, p. 41 1967
4. Forsberg S-Å., and Johnsson, G. Hemodynamic effects of propranolol and H 56/28 in man—a comparative study of two β-adrenergic receptor antagonists, Life Sc. 6 1147 1967
5. Åblad, B. Brogård, M. and Ek, L. Pharmacological properties of H 56/28—a β-adrenergic receptor antagonist, Acta pharmacol. et toxicol. 25 suppl. 2, p. 9 1967
6. Wilander B. Personal communication, 1967
7. Åkerman, B. Personal communication, 1967
8. Linko, E. Siitonen, L. and Ruosteenoja, R. A new β-adrenergic blocking agent, H 56/28, in the treatment of cardiac arrhythmias, Acta med. scandinav. 181:547 1967

Coronary care unit: A review of 300 patients monitored since 1963

Numerous publications attest the value of coronary care units for the special nursing and electrocardiographic monitoring of patients in the first few days after acute myocardial infarction.[1-4] These units not only provide an opportunity for improved patient care but their establishment has supplemented our knowledge of the pathologic physiology of acute infarction.[4] A two-bed coronary care unit was established at The Royal Melbourne Hospital in March 1963. The unit has been in continuous operation since then providing care for over 300 patients with acute myocardial infarction. During the same period of time those patients who were not admitted to the coronary care unit were cared for in standard medical wards.

The stimulus for the development of the coronary care concept came from the concurrent successful development of external cardiac massage and external electrical defibrillation. There have now been numerous reports of successful resuscitation from cardiac arrest occurring in coronary care units,[4] but the emphasis is now directed towards the prevention of cardiac arrest in patients suffering from acute myocardial infarction. A reduced incidence of primary ventricular fibrillation can be achieved by the immediate treatment of the important cardiac arrhythmias and the early treatment of cardiac decompensation.

We have reviewed our findings in 300 patients who have been treated in the coronary care unit and have compared these with the results of the management of 100 patients admitted to general ward beds during the same period, plus a further 150 patients managed in general ward beds, immediately prior to the establishment of the coronary care unit. No attempt was made to match patients for age, sex, or severity. However by classifying each patient on the basis of the first hospital examination, comparison can be obtained. The 550 patients analyzed had acute transmural myocardial infarction confirmed by serial electrocardiograms and serum enzyme studies. Electrocardiographic monitoring and special nursing care were provided in the coronary care unit for 72 hours after the last episode of chest pain or until any severe arrhythmia had been adequately controlled. All the patients in the coronary care unit were classified into three groups according to the clinical findings at the first examination in hospital. The patient's condition was classified on their admission

Table I. Comparative mortality

	Ward patients before C.C.U.		Ward patients after establishment of C.C.U.		C.C.U. patients	
	No.	Per cent	No.	Per cent	No.	Per cent
No. of "mild and severe" patients	140	91	91	91	248	83
Hospital deaths	40	28	29	31	45	18
Total	150		100		300	

as "mild severe or shocked, according t the classification of Robinson and co-workers. In the "mild" group were those patients exhibiting no evidence of shock or cardiac failure apart from a transient rise in the jugular venous pressure In the severe group were those patients with evidence of circulatory embarrassment including hypotension (systolic blood pressure less than 100 mm. Hg) and manifestations of cardiac f ilure I the shocked group were those with systolic blood pressure less than 80 mm Hg pallor or cy nosis, cold sw ating skin, and oliguria. The shocked group also included those patients adm tted t the t after cardiac arrest. Of the 300 patient managed in the coronary care It there were 145 (48.3 per cent) in the 'mild group, 103 (34 3 per cent) in the severe group and 52 (17 3 per cent) in the cardiogenic shock group.

Clinical death occurred in 67 patient while they were in the coronary care un t Eigh of these patients were resuscitated and left the hospital 23 died subsequently i general medical wards. This gave a hospital mortality rat of 82 (27 per cent).

There were 248 patient admitted t the coronary care ward in the mild" and severe groups (patients not in cardiogenic shock and not after cardiac arrest) 45 of these died in hospital—a mortality rate of 18 per cent (T ble I).

Retrospective analysis of 100 patients admitted to ward beds after the establishment of the coronary care nit howed an over-all mortality of 37 per cent This group was made up of 4 patients with mild infarction 44 patients with severe infarction nd 9 patients with cardiogenic shock. The mortality rate in the 91 patients the "mild" and severe groups was 31 per cent, compared with 18 per cent in similar coronary care u t patients

A third group of 150 patients with confirmed myocardial infarction admitted t general ward beds prior to the establishment of the coronary care unit, were analyzed i similar retrospectiv manner

Table II Serious primary arrhythmias in 300 patients with acute myocardial infarction

Arrhythmia	Classification on admission				
	Mild	Severe	Cardiogenic shock		Total
			[illegible]	b	
Atrial fibrillation	10	8	0	5	23
Supra ventricular tachycardia	2	5	0	3	10
Nodal tachycardia	10	5	0	1	16
Ventricular tachycardia and flutter	9	9	0	3	21
Second degree AV block	2	5	0	0	7
Complete heart block and AV dissociation	2	8	0	1	11
Idioventricular rhythm	0	3	0	0	3
Ventricular standstill	2	8	1	1	12
Ventricular fibrillation	4	11	0	4	19
Total					121 (40%)

Each arrhythmia recorded once only in each patient.

Table III Secondary arrhythmias in patients with cardiogenic shock

Arrhythmia	Classification on admission		
	Mild	Severe	Cardiogenic shock
Atrial fibrillation	0	1	1
Supra ventricular tachycardia	0	1	5
Nodal tachycardia	0	0	2
Ventricular tachycardia and flutter	0	1	5
Second degree AV block	0	0	0
Complete heart block nd AV dissociation	1	0	8
Idioventricular rhythm	1	1	7
Ventricular standstill	2	4	11
Ventricular fibrillation	0	1	5

Each arrhythmia recorded once only in each patient.

There were 65 patient (43 3 per cent) in the mild group 75 (50 per cent) in the severe group and 10 (6 6 per cent) in the rdiogenic shock group. The overall hospi l mortal t rat in these 150 patient was 11 per cent. The combined rates of the 140 patien m the mild nd severe groups yielded figure of 8 per ent.

There were 231 patients the mild and se ere groups of the 250 tre ted outside the coronary care nit with mortalit ra of 29 8 per cent compared with the 248 patient w th mild or severe myoc rdial f rction treated in the coronary are t w th mortal ty rat of 18 per cent. These figures suggest reduction the mortalit rates of the patient rth mild or severe myocardial infarction treated in the oronary care t.

The gre ter number of patient in the rdiogenic hock group—52 (17 3 per ent)—treated in the oronary are t reflects the endency t refer the more serious ll patient t specialized oronary re t. Of these patien s, 37 died (71 per ce t) but he mort lit rate as high irrespec tive of here tre ed. Seven of the 10 patient treated in ward bed before the est blishment of coronary re t died wh le 6 of the 9 patient treated hospital outside the oronary re t f er est l lishment of the t also died. It would appear hat pecial are did NOT produ a y improvemen in he mort lity figures in the ardiogenic hock group.

A st dy ha been made of the arious arrh thmias rring during the period of monitoring in the oronary care t. Primary arrhythmias ere defined those arrh thmia ccurring in pa ient w hout ardiogenic ho k. Secondary arrhythmias are those rrh thmia oc urring i patient with est blished ardiogenic hock being reflec ion of the seriou dist rbanc he hemod nam tat rather tha t cause. "Ser u arrh thmia were those dist bances of t hythm nd conduction pable of au ing gnifica deteriora ion the hemod namic t. W found that 40 per cent of ou patien had t le t one incident of seriou primary arrh thmia during their period of observ tion in the oronary (T ble II).

The mode of death the 67 patient ho died in the oronary re t w recorded entricula fibrilla ion in 26 en ricular t ndi ll l 16, on gestiv failure in 3 cardiogenic ho k in 19 and ruptured heart in 3. While there were ma y suc essful resuscitation effort in he u it only 8 patient left hospit l od ll of these long-term surv ors came from the group that had ent icula fibrilla tion. Primary entricul fibrillation ppear to ha become less frequen l see in the coronary nit possibl du t the mor aggressi tre tme t of premonitory rrhythmia.

Established entric la fibrillation or flutter treated w h D.C. tershock. Paroxy mal en tricular tach cardia responded ell t the use of antiarrhythmic drugs however if it became con tinuous nd w so ated w h hemodynamic deterioration immediat D.C. countershock pplied. Nodal tach card r nodal rhythm rarely caused hemod namic deterior tion nd so lly reverted spontaneously w thout pecific tre tment. Supraventricular tach ardia rred t le st once in 10 of the 300 patients. Hemodynamic deterioration in association with this rrhythmi w an indication for synchronized D.C. reversion. In other patient the dministration of digitalis nd an antiarrhythmic gent was usually sufficient. Atrial fibrillation usually is well tolerated nd does not cause hemodynamic deterioration. In all the survivors the arrhythmia reverted t dous mecha ism. Drug tre tment ppeared to ha no effect on the duration of at ial fibrillation.[14]

Seriou arrhythmias also occu in patient with ardiogenic shock however they are usually inci dental and do not affect the out ome (T ble III). Our present aim w t correct the cardiogenic shock th isoprenaline in 7 patients treated in th fashion the shock has been ontrolled nd arrhythmia has not been problem.

Our experience justifies the establishme t of special coronary re u it in all acute hospitals. Cardiogenic shock till present the greatest hal lenge the management of these patient nd f rther ork is being directed t this problem.

Graeme Sloman M.R.C.P.
M re Stannard M.B. B.S.
Ha J Goble F.R.A.C.P.
C rdiac Department
Th R yal Melbou Hospital
Australia

*Research Assistant Grant in Aid G428, National H art Foundation of Australia

REFERENCES

1. D H W An intensive coronary are area Dis. Chest 44:423, 1963
2. Brown, K W G MacMillan, R L Forbath N Mel Gr on, L and Scott J W Coronary un t A intensive care centre for acut myocardial infarction, Lancet 2 349 1963
3. Robinson J S Slom n, G nd M Rae C Continuou electrocardiogr phic mon toring in the early stages after acut m cardial infarction M J Austr lia 1 427 1964
4. J lia D G A len ine I A nd Miller C G Routine electrocardiographic monit ring in acut myocardial f rction M J Australia 1:433 1964
5. Goble A J Sloman, G nd Robinson J S Mortal ty reduction in oronary care t Brit M J 1 1005 1966
6. Low B L Klein, M Hood, W B nd Thorn, G W The co onary care t J A M A 199 188, 1967
7. M Kenzie G J T lor S H Flenley D C M Donald, A H St unton H L nd Donald, K W Circul t ry nd respira ory tudies in myocard l infarction and ardiogenic h k, Lancet 2:825 1964
8. V lentine P A Flock, D C Mounsey J P D R id, D Shillingford, J P nd Steiner R E Blood-g hanges fter ac t myocardial infarction Lancet 2:837 1966
9. J lin, M C F tannard M nd Sloman, G D turb nces f pulmona y f nction fter acut my ard l infarc ion Brit. M J 2:591 1967
10. hilling ford, J P nd Thom M Org

tion of unit for intensive care and investigation of patients with acute myocardial infarction, Lancet 2 1113, 1964
11 Thomas, M Malmcrona, R and Shillingford, J P Circulatory changes associated with systems hypotension in patients with acute myocardial infarction, Brit Heart J 28 108, 1966.
12. Julian, D G Treatment of cardiac arrest in acute myocardial ischaemia and infarction, Lancet 2:840, 1961
13. Robinson, J S Sloman, G Mathew T H and Goble A. J Survival after resuscitation from cardiac arrest in acute myocardial infarction, Am Heart J 69 740, 1965.
14 Robinson, J G., and Sloman, G. Resuscitation from cardiac arrest after acute myocardial infarction, M J Australia 1:378, 1965.
15. Stock, E Assessment of management of cardiac resuscitation, M J Australia 1:563 1966.
16. Stannard, M and Sloman, J G. Atrial fibrillation in acute myocardial infarction M J Australia 1 1250 1967

Atrial septostomy

The recent history of cardiology has been punctuated by a series of major advances, each of which has initiated a new phase of diagnostic and therapeutic activity The procedure of Rashkind and Miller whereby an atrial septal defect can be created with a balloon tipped catheter is such an advance and must rank high on the list that is headed by Blalock and Taussig Coming at a time when Mustard's[3] efforts have at last reached fruition, it offers new hope for those born with transposition of the great arteries—most of whom have circulations that are barely compatible with extrauterine life and die in the first few days or weeks of life before surgical treatment is possible. Atrial septostomy is a life-saving palliative procedure that can be performed under x-ray control on the smallest and least of babies after diagnostic cardiac catheterization without the prohibitive mortality rate associated with the surgery of cyanotic congenital heart disease at this age. Requiring only a balloon filled with angiocardiographic contrast medium at the end of a double-lumen catheter It is relatively safe remarkably well tolerated and when carried out correctly is followed by an immediate and dramatic clinical improvement

Though many patients have been successfully treated, widespread adoption of the method has been somewhat hampered by the limited supply of the special catheters that have been developed for this purpose Most failures have been due to either faulty equipment or faulty technique and are now less likely because the new catheters, which are freely available have smaller and less compressible balloons If used with the necessary vigor and initially this requires not a little courage an interatrial communication that allows satisfactory admixture of pulmonary and systemic venous blood is readily achieved in nearly all cases. While those with uncomplicated transposition are likely to benefit most, the presence of other lesions is no contraindication to septostomy and there is good evidence that it may also be of value in other conditions such as tricuspid or pulmonary atresia and total anomalous pulmonary venous return, where a larger defect in the atrial septum decompresses the right atrium and allows the venous return freer access to the left heart

The transpositions constitute the last major group of lesions awaiting relief Campbell[4] has shown, after considering all the best available evidence that 8 to 9 per cent of all babies born with serious congenital heart disease fall into this category and that at least 90 per cent of them die early figures that correspond well with the Toronto group experience and with that of Hay who found none among Liverpool school children with significant heart disease. Increased interest in the newborn period plus the stimulus of this new type of "therapeutic cardiac catheterization already suggests that the problem posed by transposition is greater than had previously been realized.

The exact role of atrial septostomy in the management of transposition of the great arteries is, of course, not yet clear Of its superiority over other palliative procedures in babies there can be no doubt because the surgical, biochemical, and respiratory hazards of opening the chest and heart are such that the mortality rate is almost prohibitive In older infants and small children who are in any case a self-selected group of survivors, the situation is different and further experience is required to decide between the relative merits of open and closed septostomy The great dividend of Rashkind' discovery will come in a few years time when a vastly larger group of live children with transposed great arteries will be available to answer the questions that will arise about their management while awaiting radical treatment

Hamish Watson, T.D M D (Edin),
F R C P.E., M R C.P
Dundee Scotland

REFERENCES

1 Rashkind, W J and Miller W M Creation of an atrial septal defect without thoracotomy A palliative approach to complete transposition of the great arteries, J A M A. 196:991 1966
2. Blalock, A and Taussig, H B The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, J A M A 128 189 1945
3. Mustard, W T Successful two-stage correction of transposition of the great vessels, Surgery 55:469 1964.
4. Aberdeen, E., Waterston D J Carr I Graham, G Bonham-Carter R. E and Subramanian, S. Successful correction of transposed great arteries by Mustard operation, Lancet 1 1233, 1965.

5. Hightower, B. M., Wendman, W. H., and Harklin, J. W.: Open intracardiac repair for complete transposition of the great arteries, Circulation 33:1, 1966.
6. Watson, H., and Rashkind, W. J.: Creation of atrial septal defect by balloon catheter in babies with transposition of the great arteries, Lancet 1:403, 1967.
7. Campbell, M., and Watson, H. (editor): A textbook of paediatric cardiology, London, 1967, Lloyd-Luke, Ltd.
8. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Co.
9. Hay, J. D.: Population and clinic studies of congenital heart disease in Liverpool, Brit. M. J. 2:661, 1966.

Coronary-artery enlargement in experimental cardiac hypertrophy*

An increase in coronary artery size (measured by a vinyl-acetate cast technique[1]) in rats submitted to hypoxia has already been demonstrated. The apparent increase in coronary-artery size preceded the development of cardiac hypertrophy. The following is a study of the effect of experimentally produced cardiac hypertrophy on coronary-artery size.

Sprague-Dawley white male rats weighing about 150 grams each were used. From each shipment of 12 rats, controls (N = 40) were chosen at random. The low-rapid weight gain of the experimental groups was simulated by means of diet in the control animals. After the animals had been painlessly put to death, vinyl acetate was injected into the aorta and filled the coronary arteries, aided by contraction of the heart. The hearts were trimmed and weighed, then placed in 35 per cent KOH. After digestion the coronary casts were trimmed and weighed in microbalance. Casts showing poor filling were discarded.

Hypoxia was produced by means of a simulated-altitude chamber made with a vacuum jar and electric pump to ensure proper ventilation. Satisfactory preparations were obtained from 57 rats subjected to 22,000 and 24,000 feet of simulated altitude for 2 hours a day for 7 to 27 days. Thyroxine 2 mg. was injected subcutaneously for 5 to 13 days, and 38 suitable preparations resulted. Aortic constriction was produced by metallic band placed round the ascending aorta and left in place for 21 to 28 days. Technically satisfactory preparations were achieved in 14 instances.

Cardiac hypertrophy (Table I) was distinct in the hypoxic and aortic-constriction groups and striking (64 per cent) in the animals injected with thyroxine. An increase in coronary-cast weight (Table I) kept pace with or exceeded the increase in heart size in all three preparations. In the hypoxic rats and those with aortic constriction there was approximately 33 per cent greater increase in coronary-cast weight than in heart weight/body weight increases. In the thyroxine-treated rats, coronary artery growth was proportionate to the rapid development of the heart muscle. Thus, at this level of cardiac hypertrophy produced by three experimental methods, there was no evidence from the coronary casts that the myocardium of the white rat began to outgrow its blood supply.

Table I. Ratios

Rat	Heart weight/ body weight (mg./g.) Means	Coronary cast/ heart weight (mg./g.×10⁻⁴) Means
Controls	366 ± 60	323 ± 94
Hypoxia	443 ± 85†	430 ± 146†
Thyroxine	596 ± 104†	314 ± 118
Aortic constriction	501 ± 74†	425 ± 115‡

*Statistical analyses by Arne Kallberger, M.D., VA Hospital, West Haven, Conn.
†p < 0.001 by t test and chi square test.
‡p < 0.01 by t test only.

Andrew Kerr, Jr., M.D.
William J. Bowen
Sam A. Pilat
Cardiopulmonary Laboratory
Veterans Administration Hospital
Boston, Mass. 02130

*Supported by a grant from the Wyoming County Heart Association and the New York Heart Assembly. J. K. Barnes, G. Green, K. W. Horsch, R. T. Howe, J. ..., and T. Tew... Research Fellows of the Heart Association of Genesee County assisted.

REFERENCES

1. Tepperman, J., and Pearlman, D.: Effect of exercise and anemia on coronary arteries of small animals as revealed by the corrosion-cast technique, Circulation Res. 9:576, 1961.
2. Kerr, A., Jr., Diasio, R. B., and Bommer, W. J.: Effect of altitude (hypoxia) on size of coronary arteries in the white rat, Am. Heart J. 69:611, 1965.
3. Kerr, A., Jr., Pilato, S., and Foster, F. J.: Coronary artery enlargement in the hypoxic white rat, Proc. Soc. Exper. Biol. & Med. 119:717, 1965.
4. Hajdu, I., and Bernak, M.: Method of producing heart hypertrophy in albino rats by narrowing the aorta ascendens, Arch. Biol. Hung. 17:213, 1947.

American Heart Journal

February 1968 Volume 75 Number 2

Editorial

Coxsackie virus infections and heart disease

Gordon C. Brown, Sc.D.
Ann Arbor, Mich.

The causative factors of most congenital anomalies remain unknown in spite of voluminous literature published on the subject during the last three decades. The relatively large number of known determinants of abnormalities, such as genetic factors, chromosomal aberrations, endocrine disturbances, drugs and chemicals, radiation, physical injury, malnutrition, and infection, although well documented, leave more than 50 per cent of anomalous births unexplained. In fact, several recent surveys have estimated that less than 2 per cent of anomalous infants were known to have been exposed to proved teratogenic agents. One of the most frequently encountered abnormal conditions of the infant is congenital heart disease. This defect has been observed to occur approximately six times in every 1,000 live births. As stated in a recent review by Higgins, the causes of malformations of the heart remain essentially unknown. The relative role of hereditary and environmental factors has been subject to considerable investigation in recent years, but with the exception of rubella virus, genetic factors, and recessive inheritance, little is known of the etiology of this condition. Furthermore, except for epidemic years, only about per cent of the malformations of the heart have been shown to be caused by rubella infections.

Other viruses, and Coxsackie viruses in particular, represent logical targets for incrimination as teratogenic agents.[4] The affinity of these infectious agents for heart tissue has become increasingly well documented in recent years. Experimental studies in young mice and in monkeys by Burch, DePasquale, and their associates have demonstrated that Coxsackie type B4 virus induces both valvular and mural endocarditis in significant numbers of infected animals. Of added significance is the fact that virus was recovered from heart tissue and was also detected in situ by the fluorescent antibody technique, which suggests strongly that the virus is capable of invading the endocardium. Lou, Wenner, and Kamitsuka[10] also produced mural endocarditis and mitral valvulitis in monkeys with this agent. Burch and his group have extended their studies to man where group B Coxsackie viruses were identified by the FA procedure in 17 of 55 hearts obtained at autopsy. A high percentage of the virus-positive specimens were from children and infants, some of whom were premature or anomalous.

The ability of these agents to cause myocarditis in adults[12] and especially in the newborn child is well documented.[13,14] Many infants with neonatal myocarditis appear to have acquired the infection during the intrauterine period and sug

From the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Mich.
Received for publication June 4, 1967.

nificantly their mothers characteristically showed no more than mild illness or completely subclinical infection.

The widespread occurrence of these infections which are predominantly subclinical in adults, the viremia which would enable such very small agents (28 mμ) to cross the placental barrier easily and the proved greater susceptibility of young rapidly metabolizing tissue to viruses all together point clearly to the fetus as a logical target for invasion and subsequent damage in the form of congenital heart disease. Evidence which strongly suggests that this is the case has recently been reported by Brown and Evans.[15] Over 10,000 pregnant women were studied prospectively and paired sera of mothers of anomalous infants together with matched specimens from mothers of normal children were tested for serologic evidence of infection with various viruses during pregnancy. A significantly greater incidence of infection with Coxsackie group B and type A9 viruses was observed in mothers of infants with congenital heart disease than in their matched controls. Types B3 and 4 were most frequently associated with malformed infant hearts. The greater frequency of maternal infection associated with abnormal infants was observed regardless of the severity of the condition which ranged from ventricular or atrial septal defects aortic or tricuspid atresia, and transposition of great vessels to mild patent ductus arteriosus and low-grade murmurs. Inclusion of this latter category was felt to be justified in view of other reports of the development of diastolic and systolic murmurs in patients several months after recovery from group B Coxsackie virus myocarditis.[1] Rubella associated congenital heart cases were discarded from the evaluation and although infections with other viruses were detected their occurrence was essentially the same in both the anomaly and the control groups.

Final proof of the incidence of congenital heart disease induced by Coxsackie virus must await extended and additional serologic studies as well as virologic evidence through isolation or visualization in affected heart tissue. In the meantime the pursuit of studies such as described herein constitutes an exciting approach to the solution of a difficult and important problem.

REFERENCES

1. Campbell, M.: Causes of malformation of the heart, Brit. M. J. 2:895, 1965.
2. McKeown, T., and Record, R. G.: Malformations in a population observed for five years after birth, Wolstenholme, G. E. W., and O'Connor, C. M., editors: Ciba Foundation Symposium on congenital malformations, Boston, 1960, Little, Brown & Company, p. 5.
3. Kerrebijn, K. F.: Incidence in infants and mortality from congenital malformations of the circulatory system, Acta paediat. scand. 55:316, 1966.
4. Higgins, I. T. T.: The epidemiology of congenital heart disease, J. Chronic Dis. 18:699, 1965.
5. Shaw, R. F.: The relative role of heredity and environment in congenital heart disease, J. Lancet 85:519, 1965.
6. Brown, G. C.: Recent advances in the viral aetiology of congenital anomalies, Advances in teratology, London, 1966, Academic Press, Inc. Vol. I, p. 55.
7. Burch, G. E., DePasquale, N. P., Sun, S. C., Mogabgab, W. J., and Hale, A. R.: Endocarditis in mice infected with Coxsackie virus B, Science 151:447, 1966.
8. Burch, G. E., DePasquale, N. P., Sun, S. C., Hale, A. R., and Mogabgab, W. J.: Experimental Coxsackie virus endocarditis, J. A. M. A. 196:349, 1966.
9. DePasquale, N. P., Burch, G. E., Sun, S. C., Hale, A. R., and Mogabgab, W. J.: Experimental Coxsackie virus B valvulitis in cynomolgus monkeys, Am. Heart J. 71:678, 1966.
10. Lou, T., Wenner, H. A., and Kamitsuka, P. S.: Experimental infections with Coxsackie viruses, Arch. Ges. Virusforsch. 10:451, 1960.
11. Burch, G. E., Sun, S. C., Colcolough, H. L., Sohal, R. S., and DePasquale, N. P.: Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques, Am. Heart J. 74:13, 1967.
12. Smith, W. G.: Adult heart disease due to Coxsackie virus group B, Brit. M. J. 2:201, 1966.
13. Kibrick, S., and Benirschke, K.: Acute aseptic myocarditis and meningoencephalitis in the newborn child infected with Coxsackie virus group B type 3, New England J. Med. 255:883, 1956.
14. Kibrick, S., and Benirschke, K.: Severe generalized disease (encephalohepatomyocarditis) occurring in the newborn period and due to infection with Coxsackie virus, group B: evidence of intrauterine infection with this agent, Pediatrics 22:857, 1958.
15. Brown, G. C., and Evans, T. N.: Serologic evidence of Coxsackie virus etiology of congenital heart disease, J. A. M. A. 199:183, 1967.
16. Babb, J. M., Stoneman, M. E. R., and Stern, H.: Myocarditis and croup caused by Coxsackie virus type B, Arch. Dis. Child. 36:551, 1961.

Clinical communications

The vectorcardiographic patterns of unusual conduction disturbance in infancy and childhood

George H Khoury M.D
Rodney S Fowler M.D
Morgantown W Va

The vectorelectrocardiographic patterns of conduction disturbances involving the terminal cardiac vectors (rsR') in infancy and childhood have been well documented in the literature in the different types of congenital heart disease. On the other hand reports concerned with the vectorcardiographic picture of abnormalities in the direction of the 0.02 second QRS vector as well as the body of the QRS loop in conditions other than anomalous origin of the left coronary artery are limited.[1-3]

It is the purpose of this communication (1) to describe the Frank vectorcardiogram (VCG) and the scalar electrocardiogram (ECG) in eight patients with different clinical and hemodynamic profiles who exhibited unusual abnormalities in the direction of the initial vectorial forces simulating myocardial infarction patterns and (2) to point out the value of the VCG in delineating the abnormal early depolarization vectors in patients with pathologic deep Q waves in the ECG not thought diagnostically specific.

Materials and methods

The basic material comprises the VCG's recorded with the Frank corrected lead system and the scalar ECG's in eight patients, varying in age from three months to fourteen years, admitted to the hospital for Sick Children in Toronto Canada. The patients were divided into two main groups according to the basic cardiac abnormalities.

Group 1 included four patients with myocardial disease. This group was further divided into two subgroups according to the types of vector loops encountered.

Subgroup 1a included three infants (Cases 1, 2 and 3) in whom the clinical picture was more or less similar. Their ages were 3, 6 and 4 months, respectively. They were admitted to the hospital in severe congestive heart failure. On physical examination the heart was markedly enlarged and overactive. The heart sounds were of poor quality. No murmurs were heard. The liver was enlarged and tender. The chest roentgenograms in all three cases showed gross cardiac enlargement but normal pulmonary vascularity with cardiothoracic ratio over 65 per cent. Right and left cardiac catheterization were performed. The findings were within normal limits except for a high left ventricular end diastolic pressure of 20 mm Hg in Case 1. No gradient across the aortic valve was found in any of the instances. Left ventricular cine-

From the Department of Cardiology and Research Institute, the Hospital for Sick Children, Toronto, and the Department of Pediatrics, University of Toronto, Toronto, Ont., Canada.
Supported by grant from the Ontario Heart Foundation.
Received for publication April 3, 1967.
Address: West Virginia University Medical School, Department of Pediatrics, Morgantown, W. Va.

angiogram was done in Cases 1 and 2. It showed a large left ventricle which contracted poorly. Retrograde aortogram was done in all and revealed a normal coronary arterial pattern.

The clinical diagnosis (possible endocardial fibroelastosis) in the three cases was diffuse cardiomyopathy.

Subgroup 1b included one patient, 11 months old (Case 4). She was admitted to the hospital with a history of frequent respiratory infections, irritability, and vomiting of 48 hours' duration. On physical examination she appeared severely ill with marked dyspnea. The heart tones were poor. A gallop rhythm was present but no murmurs were heard. The chest roentgenogram showed a very large heart with a cardiothoracic ratio of 65 per cent. The patient responded dramatically to the administration of digitalis, diuretics, and oxygen. The clinical diagnosis was myocarditis.

Group 2 included four patients with complex congenital heart disease. Cases 5, 6, and 7 had tricuspid atresia with normally related great vessels, ventricular septal defect, and pulmonary stenosis (Type 1b). Their ages were 2 months, 10 and 14 years respectively. One patient 7 months old (Case 8) had complete transposition of the great vessels and had been reported upon previously. The diagnosis was confirmed by hemodynamic, angiocardiographic studies, and surgery.

Electrocardiographic findings

In Group 1, the tracings were obtained before instituting therapy (Table I). In Subgroup 1a, the ECG was consistent with left ventricular hypertrophy in all three cases as indicated by a deep S wave in the right precordial leads and a tall R wave in Lead V6. An abnormal deep Q wave was present in V V and V6. The T wave was either diphasic or inverted in Leads I, II, V5 and V (Figs. 1 and 2).

In Subgroup 1b, the ECG showed abnormal T waves, low voltage throughout with a flat and inverted T wave consistent with the diagnosis of myocarditis in Case 4 (Fig. 3). This ECG corresponds to the VCG recorded at the top of Fig. 5.

In Group 2, the ECGs were taken while the patients were on digitalis. They showed evidence of left ventricular hypertrophy, but no deep Q wave was noted in the left precordial leads. T wave inversion was present in Leads I, V5, and V6 (Fig. 4).

Vectorcardiographic findings

Group 1. Patients with myocardial disease.

SUBGROUP 1A. In the frontal plane, the

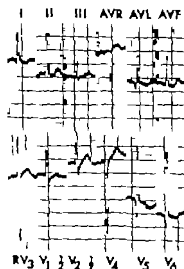
Table I Electrocardiographic findings

Case	Age	Heart rate	P-R interval	P wave height (mm)	Frontal axis QRS	QRS duration	Precordial leads R/S ratio V1	Precordial leads R/S ratio V6	Abnormal Q waves
Group 1									
P B	3 m	150	0 10	2	+20	0 10	5/32	32 0	V V V
B M	6 mo	160	0 08	1	+60	0 08	16/28	17 0	V V V
D B.	4 mo.	170	0 16	1	+20°	0 08	6/20	25 0	V V V
M F	11 mo.	150	0 16	4	+100°	0 06	4/2	13/[illegible]	— — —
Group 2									
L L	2 [illegible]	160	0 10	4	−1[illegible]	0 06	1 4	8 0	– —
L D	10 y	80	0 12		+20	0 08	5/30	33/	
B C	14 y	80	0 14	3	−30	0 10	5 [illegible]	32/1	– –
Y S	[illegible] mo	170	0 1	2	0°	0 06	15 30	8 1	— — —

QRS loop was counterclockwise in Cases 1 and 2 (Fig 1) and had a figure of eight in Case 3 (Fig 2) The half area QRS vector was directed to the left and inferiorly The mean magnitude of the maximum QRS vector was 2 3 mv

In the horizontal plane the initial 0 01 second QRS vector was normal in direction The 0 02 second QRS vector was directed to the right and anteriorly in Cases 1 and 3 and posteriorly in Case 2 (Figs. 1 and 2) the reverse of normal. Then the QRS loop continued in a clockwise trajectory with the half area QRS vector directed to the left and posteriorly The mean magnitude of the maximum QRS vector was 2 8 mv The maximum T vector was directed anteriorly in the +90 degrees axis in Cases 1 and 2 to the right and posteriorly in Case 3 In the left sagittal plane, the QRS loop was inscribed clockwise in Cases 2 and 3 and had a figure of eight in one The QRS loop was placed mainly posteriorly and inferiorly The mean magnitude of the maximum QRS vector was 2 6 mv The VCG was indicative of anterolateral infarction plus left ventricular myocardial hypertrophy

SUBGROUP 1B The VCG taken on admission was markedly abnormal The initial QRS vectors (Fig 5a) in the horizontal plane were normal in direction but the QRS loop continued in a clockwise inscription, directed posteriorly in the midline, with crossovers in the middle and terminal part of the loop with terminal delayed conduction This was also evident in the frontal and left sagittal planes The ECG and VCG (Fig 5b) taken four weeks later showed the evolution to a normal pattern The clinical diagnosis in this case was myocarditis.



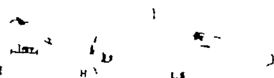


Fig 1 The ECG and VCG in Case 2 Notice in the ECG the rS pattern in V and deep Q V is greater than I V I the horizontal plane the 0 02 second QRS vector directed to the right and anteriorly the reverse of normal The QRS loop is clockwise and directed the left and posteriorly The VCG is consistent with anterior myocardial infarction plus left ventricular hypertrophy

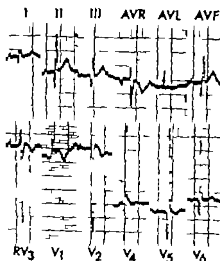




Fig 2 The ECG and VCG Case 3 The Q is more deep in V and V than V The ECG is consistent with the left ventricular hypertrophy Notice I the horizontal plane of the VCG the abnormal orientation of the 0 02 second QRS vector and the 0 02 second QRS vector with the clockwise inscription of the QRS loop. The VCG is suggestive of anterior myocardial infarction and left ventricular hypertrophy

Group 3. Patients with complex congenital heart disease. In the frontal plane, the QRS loop was counterclockwise in all cases (Fig. 4). The half area QRS vector was directed to the left and superiorly in Cases 5, 6, and 8, inferiorly in Case 7. The mean magnitude of the maximum QRS vector was 1.8 mv. In the horizontal plane the 0.02 second QRS vector was oriented to the right and posteriorly, the reverse of normal, but the QRS loop continued counterclockwise. The maximum vector was directed to the left and posteriorly and its mean magnitude was 3.0 mv. The maximum T vector was directed to the right and anteriorly. In the left sagittal plane the QRS loop was counterclockwise in all cases. The half area vector was directed posteriorly either superiorly or inferiorly. The mean magnitude of the maximum QRS vector was 2.8 mv.

Discussion

Three types of abnormal vector loops delineating altered direction of the initial and main forces of ventricular depolarization have been described in this study.

In the Type 1 horizontal plane, the QRS loop was clockwise and oriented to the left and posteriorly with increased magnitude of the maximum QRS vector. Such a pattern is consistent with antero-lateral myocardial infarction and when observed in infancy it is suggestive, but not diagnostic, of anomalous origin of the left coronary artery as claimed in previous reports.[5-7] Similar vectorcardiographic patterns have been described by Elliott and his associates[1] in a patient with a developmental anomaly of the left ventricle and by Lintermans and his associates[3] in three patients with endocardial fibroelastosis. This study corroborates their findings.

The scalar ECG in patients with diffuse cardiomyopathy was consistent with left ventricular hypertrophy. The clue to the presence of altered direction observed in the VCG is an abnormally deep Q wave in V and V_6. The presence of pathologic deep Q wave in the left precordial leads is always subject to various interpretations and its diagnostic implication is usually not specific. Recently Braudo and associates[8] have reported abnormal deep Q wave in children with muscular subaortic stenosis and attributed it to marked ventricular septal hypertrophy. However, the VCG presented in their study did not show any conduction defect. Pruitt and co-workers[9] have described electrocardiographic findings simulating apicolateral wall infarction in patients with myocardial destructive lesions unrelated to occlusive coronary arterial disease. It is apparent that more

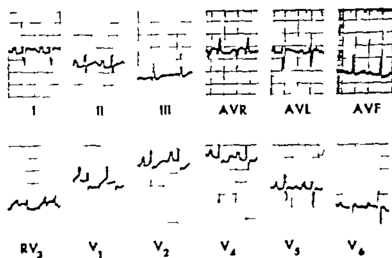


Fig. 3. The ECG of Case 4 corresponding to the VCG recorded at the top of Fig. 5. P-R interval 0.16 second. Abnormal Q waves are present in Leads II, RV, V and V. Note the flattened T waves throughout the tracing.

vectorcardiographic studies are needed in patients who exhibit deep Q waves in the scalar ECG in order to evaluate both the diagnostic and prognostic importance of these myocardial infarction patterns.

In the Type 2 vector loop the initial vectors were normal in direction but the main QRS showed multiple crossover in the three planes with decreased magnitude of the spatial maximum QRS vector and terminal delayed conduction. The pattern was seen in one patient with myocarditis.

In the Type 3 vector loop the 0.02 second QRS vector in the horizontal plane was reversed in direction initially clockwise, but the QRS loop continued in a counterclockwise inscription projected to the left and posteriorly. This type also resembles patterns of anterior myocardial infarction. It has been reported previously in patients with tricuspid atresia,[1-3] but to our knowledge no one has observed it in complete transposition of the great vessels. In patients with Type 2 VCG no evidence was found in their ECG to suspect any conduction defect.

The pathogenesis of such vectorcardiographic patterns in the absence of true

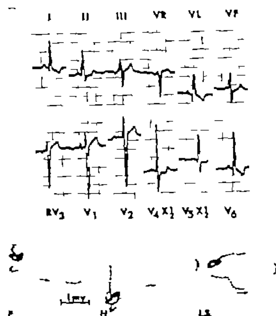


Fig. 4. The ECG and VCG in a patient with tricuspid atresia (Case 6). The ECG is consistent with left ventricular hypertrophy. No abnormal Q waves were seen in the left precordial leads.

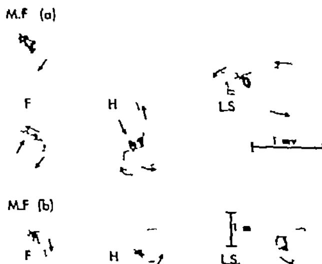


Fig. 5. A, The VCG in Case 8 taken on admission. The initial vectors are normal in direction. The main QRS loop showed multiple crossover with terminal conduction delay in the three planes. B, The VCG taken four weeks later. It shows the evolution to a normal pattern.

myocardial infarction is still obscure. It has been attributed to advanced left ventricular hypertrophy, myocardial fibrosis,[1] and hypoplasia of the right ventricle with lack of significant right septal dipoles[3] in cases of tricuspid atresia.

To conclude, the vectorcardiographic patterns of myocardial infarction do occur in conditions other than anomalous origin of the left coronary artery, such as diffuse cardiomyopathy, endocardial fibroelastosis, myocarditis, and complex cardiac malformations.

Summary

The vectorelectrocardiographic patterns of conduction disturbances involving the initial cardiac vectors and the body of the QRS loop have been described in eight patients with different cardiac abnormalities.

In three patients with the clinical diagnosis of diffuse cardiomyopathy, the VCG showed a clockwise QRS loop in the horizontal plane which was oriented to the left and posteriorly, a pattern of anterior myocardial infarction. In one patient with myocarditis, the VCG was markedly abnormal and its evolution to normal pattern was presented.

In three patients with tricuspid atresia and one with complete transposition of the great vessels, the 0.02 second QRS vector in the horizontal plane was oriented to the right and anteriorly or posteriorly, the reverse of normal, a pattern suggestive of myocardial infarction.

REFERENCES

1. Elliott, L. P., Ruttenberg, H. D., and Tuna, N.: Unusual conduction disturbances in congenital cardiac disease, Am. J. Cardiol. 12:753, 1963.
2. Lintermans, J. P., Kaplan, E. L., Morgan, B. C., Baum, D., and Guntereth, W. G.: Infarction patterns in endocardial fibroelastosis, Circulation 33:202, 1966.
3. Gamboa, R., Gersony, W. M., and Nadas, A. S.: The electrocardiogram in tricuspid atresia and pulmonary atresia with intact ventricular septum, Circulation 31:24, 1966.
4. Khoury, G. H., Shaher, R. M., and Fowler, R. S.: The vectorcardiogram in complete transposition of the great vessels. Analysis of 50 cases, Circulation 35:178, 1967.
5. Noren, R. G., Raghib, G., Moller, J. H., Amplatz, K., Adams, P., Jr., and Edwards, J. E.: Anomalous origin of the left coronary artery from the pulmonary trunk with special reference to the occurrence of mitral insufficiency, Circulation 30:171, 1964.
6. Nadas, A. S., Gamboa, R., and Hugenholtz, P. G.: Anomalous left coronary artery originating from the pulmonary artery, Circulation 29:167, 1964.
7. Puri, P. S., Rowe, R. D., and Neill, C. A.: Varying vectorcardiographic patterns in anomalous left coronary artery arising from pulmonary artery, Am. Heart J. 71:616, 1966.
8. Braudo, M., Wigle, E. D., and Keith, J. D.: A distinctive electrocardiogram in muscular subaortic stenosis due to ventricular septal hypertrophy, Am. J. Cardiol. 14:599, 1964.
9. Pruitt, R. D., Curd, G. W., Jr., and Leachman, R.: Simulation of electrocardiogram of apicolateral myocardial infarction by myocardial destructive lesions of obscure etiology (Myocardiopathy), Circulation 25:506, 1962.
10. Cabrera, E., and Gaxiola, A.: Diagnostic contribution of the vectorcardiogram in hemodynamic overloading of the heart, Am. Heart J. 60:296, 1960.

Basal diastolic murmurs in rheumatic heart disease: Intracardiac phonocardiography and cineangiography

*Vincent Russo, M.D.**
*Hugh S. Levin, M.D.***
*Hussein Vakabzadeh, M.D.****
*Richard W. Booth, M.D.*****
Omaha, Neb.

Previous studies[1-4] have convincingly shown that the great majority of patients with mitral stenosis and a basal diastolic murmur have demonstrable aortic regurgitation in spite of clinical evidence favoring relative pulmonic insufficiency. Most of the reports, however, including our own, failed to adequately evaluate the competency of the pulmonic valve. Many techniques previously used to detect pulmonic regurgitation have not proved entirely satisfactory and the demonstration of aortic regurgitation alone does not preclude coexisting pulmonic insufficiency. In addition, many of the previously reported cases with a basal diastolic murmur and proved aortic regurgitation did not fulfill all the diagnostic criteria currently required to make the diagnosis of a Graham Steell murmur.

The purpose of the present study was threefold: (1) to more clearly define the origin and significance of basal diastolic murmurs in rheumatic heart disease, (2) to evaluate the reliability of intracardiac phonocardiography and angiography in the detection of pulmonary valve incompetence, and (3) to assess the presence or absence of pulmonic insufficiency and its incidence in patients with mitral stenosis and all the generally accepted criteria for a Graham Steell murmur.

Material and methods

The material for this study includes 15 patients with rheumatic heart disease, severe mitral stenosis, a Grade I to III out of VI high-pitched blowing decrescendo basal diastolic murmur (heard only along the left sternal border), and clinical evidence of pulmonary hypertension later confirmed by catheterization studies. The evidence for pulmonary hypertension in all patients included (1) a prominent right ventricular impulse and a markedly accentuated pulmonic closing sound on physical examination, (2) right ventricular enlargement and enlarged main pulmonary arteries on x rays

From the Department of Medicine, Division of Cardiology, Creighton University School of Medicine, Omaha, Neb.
Presented at the first meeting of the Laennec Cardiovascular Sound Group, October 4, 1965, Bal Harbour, Fla.
Supported in part by the United States Public Health Service Grant (HE-[illegible]), National Institutes of Health, Bethesda, Md., and the Nebraska Heart Association.
Received for publication April 8, 1967.

*Associate Professor of Medicine, Creighton University School of Medicine.
**Associate Professor of Medicine, Creighton University School of Medicine.
***Teheran, Iran.
****Professor of Medicine, Creighton University School of Medicine, Director, Cardiac Laboratory, St. Joseph Hospital, 2305 South 10th St., Omaha, Neb. 68108.

myocardial infarction is still obscure. It has been attributed to advanced left ventricular hypertrophy myocardial fibrosis, and hypoplasia of the right ventricle with lack of significant right septal dipoles[2] in cases of tricuspid atresia.

To conclude the vectorcardiographic patterns of myocardial infarction do occur in conditions other than anomalous origin of the left coronary artery such as diffuse cardiomyopathy endocardial fibroelastosis, myocarditis, and complex cardiac malformations.

Summary

The vectorelectrocardiographic patterns of conduction disturbances involving the initial cardiac vectors and the body of the QRS loop have been described in eight patients with different cardiac abnormalities.

In three patients with the clinical diagnosis of diffuse cardiomyopathy the VCG showed a clockwise QRS loop in the horizontal plane which was oriented to the left and posteriorly a pattern of anterior myocardial infarction In one patient with myocarditis, the VCG was markedly abnormal and its evolution to normal pattern was presented

In three patients with tricuspid atresia and one with complete transposition of the great vessels, the 0 02 second QRS vector in the horizontal plane was oriented to the right and anteriorly or posteriorly the reverse of normal a pattern suggestive of myocardial infarction.

REFERENCES

1 Elliott L. P Ruttenberg, H. D and Tuna, N Unusual conduction disturbances in congenital cardiac disease, Am. J Cardiol. 12 753 1963.

2 Lintermans, J P Kaplan, E. L. Morgan, B C., Baum, D and Gunteroth, W G.: Infarction patterns in endocardial fibroelastosis, Circulation 33:202, 1966.

3. Gamboa, R. Gersony W M and Nadas, A. S. The electrocardiogram in tricuspid atresia and pulmonary atresia with intact ventricular septum, Circulation 31:24 1966.

4 Khoury G H Shaher R. M and Fowler R. S. The vectorcardiogram in complete transposition of the great vessels Analysis of 50 cases, Circulation 35 178, 1967

5. Noren, R G Raghib, G., Moller J H., Amplatz, K. Adams, P J and Edwards, J E. Anomalous origin of the left coronary artery from the pulmonary trunk with special reference to the occurrence of mitral insufficiency Circulation 30 171 1964.

6. Nadas, A. S., Gamboa, R., and Hugenholtz, P G Anomalous left coronary artery originating from the pulmonary artery Circulation 29 167 1964.

7 Puri, P S Rowe R D and Neill, C. A. Varying vectorcardiographic patterns in anomalous left coronary artery arising from pulmonary artery Am. Heart J 71:616 1966

8. Braudo, M Wigle, E. D and Keith, J D A distinctive electrocardiogram in muscular subaortic stenosis due to ventricular septal hypertrophy Am. J Cardiol. 14:599 1964

9 Pruitt, R. D Curd, G W J and Leachman, R. Simulation of electrocardiogram of apicolateral myocardial infarction by myocardial destructive lesions of obscure etiology (Myocardiopathy) Circulation 25:506, 1962.

10. Cabrera, E., and Gaxiola, A.: Diagnostic contribution of the vectorcardiogram in hemodynamic overloading of the heart, Am. Heart J 60:296 1960.

N I H catheter were both advanced to the main pulmonary artery in the conventional manner The micromanometer was then withdrawn to the right ventricular outflow tract where simultaneous sound and pressure were recorded A diastolic murmur of pulmonic regurgitation due to valvular distortion by the N I H catheter in the pulmonary artery was almost invariably detected by the micromanometer in the right ventricle. This was especially true when the tip of the N I.H catheter was close to the pulmonary valve. Without changing the position of the micromanometer the diastolic murmur immediately disappeared when the N I.H catheter was withdrawn to the right ventricle or atrium (Fig 1)

To demonstrate visually the pulmonic regurgitation due to valvular distortion by a catheter and to substantiate further the reliability of the phonocatheter to detect the regurgitation conventional cinepulmonic valvulography was performed in the dogs with an N I H catheter in the pulmonary artery while sound and pressure

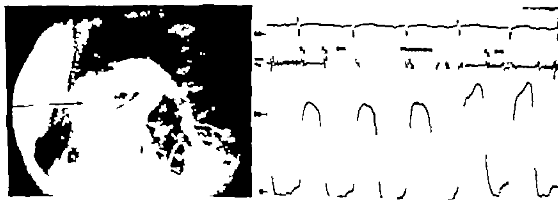


Fig 2 *A* Conventional pulmonic valvulography in dog demonstrating false pulmonic regurgitation (arrow). The micromanometer tip is in the right ventricular outflow tract. The N I H catheter tip is in the main pulmonary artery *B* The micromanometer recording during the cineangiogram shown in *A* Noise artifact is produced by the pressure injection of contrast media. A diastolic murmur is shown prior to and following the injection.

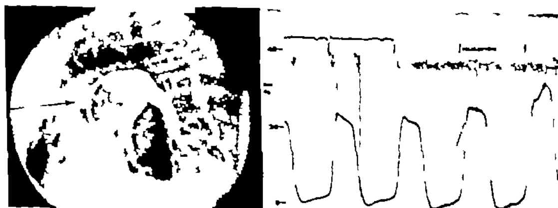


Fig 3 *A* Pulmonic valvulography in dog in which pulmonic regurgitation did not occur The arrow indicates the micromanometer in the right ventricular outflow tract. *B* The micromanometer recording from the right ventricular outflow tract during the cineangiogram shown in *A* No diastolic murmur was detected before or after the injection.

were recorded by the micromanometer in the right ventricular outflow tract. One-half to one c.c. per kilogram of body weight of contrast medium (Renovist) was injected at 6 to 7 Kg. per square centimeters of pressure through the NIH catheter positioned in the main pulmonary artery and cine film taken at 30 or 60 frames per second. Pulmonic regurgitation demonstrated angiographically was readily detected by the intracardiac micromanometer (Fig. 2), whereas no diastolic murmur was recorded if pulmonic regurgitation did not occur (Fig. 3). The results of these studies were consistent in over 60 animal experiments and confirmed the reliability of the phonocatheter in detecting even minor degrees of pulmonic regurgitation demonstrated cineangiographically. These studies alerted us, however, to some possible pitfalls of intracardiac phonocardiography. Care must be taken to position the micromanometer high in the outflow tract, since a regurgitant murmur may be missed if the tip is not in the regurgitant stream. In addition, some low frequency diastolic vibrations are occasionally recorded by the micromanometer alone in the right ventricle, but slight repositioning of the phonocatheter or careful analysis of the recorded tracing will usually prove these to be artifacts.

Patient studies. To evaluate the competency of the pulmonic valve by intracardiac phonocardiography in the patients comprising this study, the Allard Laurens micromanometer was used to assess the presence or absence of a pulmonic regurgitant murmur in the right ventricular outflow tract immediately proximal to the pulmonic valve. Although intracardiac phonocardiography does not always precisely localize sound to the cardiac chamber from which it arises, we have not as yet been able to record aortic diastolic murmurs of even grade 5 intensity from the right ventricle by this technique. The micromanometer was first advanced to the pulmonary artery and its zero pressure reference established with an external Statham transducer connected to the side opening lumen of the phonocatheter. Simultaneous intracardiac sound and pressure were then continuously recorded by an Electronics for Medicine oscillographic recorder while the micromanometer was slowly withdrawn through the pulmonic valve to the high right ventricle. The recordings were made at paper speeds of 50 to 100 mm. per second with the electron sweep limited to two or four channels to obtain maximum frequency response for the sound tracings. The pullback procedure was usually repeated several times, especially if artifacts or arrhythmias prevented a satisfactory recording high in the outflow tract. The recording was then continued while the micromanometer was further withdrawn to the right atrium.

The second method used to evaluate pulmonary valve competency in the patient study was cinepulmonic valvulography. To avoid the catheter induced false regurgitation previously discussed, the conventional technique was modified. If the electrical output of the marker circuit from a Cidlund power injector is connected to a D.C. amplifier channel on the Electronics for Medicine recorder, movement of the pump piston during injection will produce a deflection on the oscillographic screen. By marking the predetermined end of this deflection

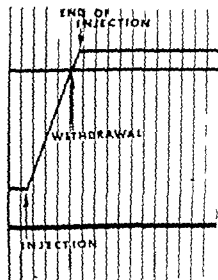


Fig. 4. The deflection produced by movement of the power injector pump piston during injection. The second electron beam is positioned below the predetermined end of deflection to allow for human reaction time. The catheter withdrawal is begun when the piston deflection reaches the second electron beam.

(the end of the injection) with a second electron beam and allowing some delay for human reaction a standard N I H catheter can be rapidly withdrawn from the pulmonary artery to the right atrium or superior vena cava immediately following the end of the injection of contrast medium (Fig 4) Usually 40 to 45 c.c. of contrast media are injected at 6 to 7 Kg per square centimeters of pressure through a No 6 or No. 7 N I H catheter and cine film taken at 30 or 60 frames per second In patients with pulmonary hypertension or with marked regurgitation from congenital pulmonic insufficiency the pulmonic valve can be visualized for several diastolic phases following the end of the injection and catheter withdrawal. Its competency can then be assessed without interference by the catheter (Fig 5) In patients without pulmonary hypertension or gross regurgitation however the technique may not be reliable since rapid clearing of the contrast media from the main pulmonary artery may not permit satisfactory visualization of the valve following withdrawal of the catheter

Results

Using the methods described we were able to demonstrate pulmonic regurgitation in only one of the 15 patients, and this was shown by both modified pulmonic valvulography and intracardiac phonocardiography Aortic valvulography on the other hand demonstrated aortic regurgitation in all 15 patients including the one with pulmonic insufficiency The severity of aortic regurgitation varied from 1 to 3+ on a 0 to 4+ scale.

The one patient (O M) with pulmonic insufficiency was a 3? year-old Indian woman with clinical findings similar to the rest of the group previously described The ECG demonstrated right ventricular hypertrophy At catheterization the pulmonary artery pressure was 80 40 mm Hg at rest and the calculated mitral valve area was 0 6 sq cm which was later confirmed at surgery A decrescendo diastolic murmur following a loud pulmonic closing sound was repeatedly recorded by the intracardiac micromanometer in the high right ventricle (Fig 6) The modified technique for cinepulmonic valvulography was performed with 40 c c. of contrast medium injected at 7 Kg per square centimeter pressure through a No 6 N I H catheter Pulmonic regurgitation was demonstrated angiographically with the catheter still positioned in the pulmonary artery but was also seen for several diastolic phases following the catheter withdrawal to the superior vena cava at the end of the injection (Fig 7) Aortic valvulography demonstrated an incompe



Fig 5 A The pulmonic regurgitation (arrow) in patient during pulmonic valvulography while the N I H catheter is in the pulmonary artery B Visualization of the pulmonic valve without regurgitation in the same patient during diastolic phase following the end of injection and catheter withdrawal. The I C phonocatheter in later study did not detect pulmonic regurgitation in this patient.

tent aortic valve as well with 2+ aortic regurgitation

The standard ECG's and right ventricular micromanometer sound and pressure recordings of three other patients from the study are shown in Fig 8. These records are examples to illustrate the findings in the 14 patients *without pulmonic regurgitation*. Each had evidence of right ventricular hypertrophy on the ECG and significant pulmonary hypertension at catheterization with right ventricular systolic pressures from 65 to 100 mm. Hg at rest. Not one had a pulmonic regurgitant murmur in the right ventricular outflow tract

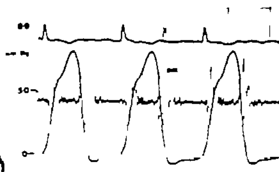


Fig. 6 The micromanometer simultaneous sound and pressure recording from the right ventricle in patient O. M. demonstrating the decrescendo diastolic murmur of pulmonic regurgitation.

on repeated micromanometer pullback recordings across the pulmonic valve. Cinepulmonic valvulography by the modified technique in these patients also demonstrated a competent pulmonary valve. All three patients were shown to have aortic regurgitation.

In addition to the 15 patients described above nine other patients with mitral stenosis and a basal diastolic murmur were studied. These patients also had clinical evidence of pulmonary hypertension right ventricular enlargement on x rays, and tight mitral stenosis by left heart catheterization studies. The basal diastolic murmur was heard only along the left sternal border and none had evidence of dynamic aortic regurgitation aortic stenosis, or left ventricular enlargement by physical examination fluoroscopy or ECG's. Although the basal diastolic murmur in these nine patients could readily have been attributed to relative pulmonic insufficiency by clinical criteria, they were not included with the other 15 patients because either they did not have definite electrocardiographic evidence of right ventricular hypertrophy or the right ventricular pressure during right heart catheterization was less than 60 mm. Hg at rest. Using the same techniques previously described all nine patients were shown to have aortic regurgitation while none



Fig. 7 A Pulmonic regurgitation (arrow) in patient O. M. while the NIH catheter is in the pulmonary artery B The pulmonic regurgitation (arrow) was still demonstrated for several diastolic phases following the end of injection and catheter withdrawal to the superior vena cava.

had evidence of pulmonary valve incompetence by intracardiac phonocardiography or modified cinepulmonic valvulography

Discussion

The murmur of relative or functional pulmonic insufficiency due to high pressure in the pulmonary artery was first described by Graham Steell in 1888.[3] Relative pulmonic insufficiency became a well accepted clinical entity and in the past, was generally considered the origin of a basal diastolic murmur in patients with mitral stenosis and clinical evidence of pulmonary hypertension in the absence of signs indicating aortic regurgitation. For over half a century the Graham Steell murmur was considered a common finding occurring in as high as 10 to 15 per cent of patients with mitral stenosis. This incidence was seriously questioned however by the frequency with which unsuspected aortic regurgitation was demonstrated in a previous study of patients thought clinically to have relative pulmonic insufficiency. Although the competency of the pulmonic valve was not evaluated in that report we concluded that the incidence of the Graham Steell murmur in rheumatic heart disease had been greatly exaggerated and doubted the reliability with which it could be differentiated from adynamic aortic regurgitation by clinical evaluation alone. The results of other similar studies appeared to support these conclusions.

More recently however Cohn and Hultgren[7] reported three "established examples of the Graham Steell murmur which they had correctly recognized by clinical evaluation alone. They emphasized the points that relative pulmonic insufficiency in rheumatic heart disease is a clinically identifiable entity and that most of the previously reported cases that proved to have aortic regurgitation did not fulfill their diagnostic criteria for a Graham Steell murmur. Although these three cases may represent instances in which the Graham Steell murmur was correctly recognized clinically it should be noted that objective studies to evaluate the competency of either the aortic or pulmonic valve under normal physiologic conditions were totally lacking. Their proof for the presence of relative pulmonic insufficiency was based on failure to detect aortic regurgitation during cardiopulmonary bypass and the diminution or disappearance of the basal diastolic murmur following surgery.

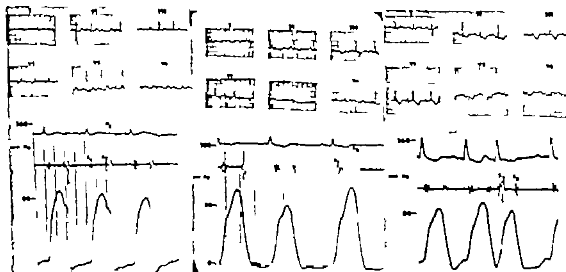


Fig. 3. The standard ECG and micromanometer sound and pressure recordings from the right ventricular outflow tract of three other patients in the study. \ diastolic murmurs of pulmonic regurgitation were detected.

The 15 patients included in the present report satisfy all the criteria for a Graham Steell murmur including documented pulmonary hypertension by catheterization studies. An additional nine patients with clinical findings at least favoring relative pulmonic insufficiency as the source of a basal diastolic murmur were also studied. In only one instance, however, was pulmonic regurgitation detected by intracardiac phonocardiography or by modified cinepulmonic valvulography. On the other hand, all 24 patients, including the one with pulmonic regurgitation, had demonstrable aortic regurgitation by angiography. These results would support our previous conclusions that relative pulmonic insufficiency is rarely the source of a basal diastolic murmur in rheumatic heart disease and that it cannot, at least from our experience, be clinically differentiated from adynamic aortic regurgitation regardless of criteria used.

Our failure to assess pulmonic regurgitation in earlier studies of the basal diastolic murmur in rheumatic heart disease was due primarily to the lack of practical and reliable methods of evaluation. Cineaortic valvulography, properly performed and critically interpreted, is generally accepted as a reliable means for evaluating aortic regurgitation. A single method for assessing pulmonary valve incompetence, however, is not so widely used or accepted. A number of indicator techniques, pulmonary angiography, pulmonary artery pressure curve analysis, and the administration of drugs, such as amyl nitrite, vasopressors, reserpine, and serotonin, have been used to detect pulmonic regurgitation. All may give erroneous results, however, especially when evaluating minor degrees of regurgitation or in the case of drug administration when cardiac failure, severe pulmonary hypertension, or incompetence of both semilunar valves exist, as was found in the one patient with pulmonic regurgitation in this study.

Conventional cinepulmonic valvulography with good visualization of the pulmonary valve and a negative result is reliable, but false positive results from valvular distortion by a catheter may be frequent. This was shown in the present experimental and patient study, and we have noted it frequently with pulmonary angiography in other patients with presumably normal pulmonary valves. Catheter-induced false pulmonic regurgitation has also been reported by others.[4,5] A suprasternal percutaneous needle approach for pulmonic valvulography was reported by Brest, Udhoji, and Likoff, and its reliability was confirmed by our own studies in normal dogs demonstrating false regurgitation with conventional pulmonic valvulography, but not by a transthoracic approach with a needle. We found this method technically difficult, however, and because of significant hazard we have not used it in our patient studies. The withdrawal modification described in this report avoids many of the limitations of previous pulmonic valvulography techniques. Unfortunately, it may not be reliable in patients without pulmonary hypertension unless gross regurgitation exists. The need for exact timing of the catheter withdrawal and the potential hazards of angiography in general further limit its usefulness.

Intracardiac phonocardiography already proved as a valuable tool in cardiac diagnosis, has been used to detect congenital pulmonic regurgitation and pulmonic regurgitation following bacterial endocarditis,[11] and pulmonary valve surgery.[2] Pulmonic insufficiency associated with acquired mitral stenosis and pulmonary hypertension has also been convincingly demonstrated with intracardiac phonocardiograms by both Soulie and his associates[13] and by Lumada.[12] From our previous experience and the results of the present study, we find intracardiac phonocardiography a safe, simple, and reliable method for evaluating the competency of the pulmonic valve and prefer it to any of the other techniques described.

Summary and conclusions

This study was undertaken to further evaluate angiography and intracardiac phonocardiography in assessing the competency of the pulmonic valve and to better define the origin and significance of basal diastolic murmurs and the true incidence of pulmonic insufficiency in patients with mitral stenosis and pulmonary hypertension.

From the results of this study, we have

reached the following conclusions (1) conventional pulmonic valvulography often produces false regurgitation which may be avoided by the withdrawal modification (2) intracardiac phonocardiography is reliable for assessing pulmonary valve competency (3) aortic regurgitation is almost invariably the source of basal diastolic murmurs in patients with mitral stenosis, and finally (4) relative pulmonic insufficiency in spite of clinical evidence for its existence is truly a rarity in rheumatic heart disease

REFERENCES

1. Runco, V, Molnar W, Meckstroth, C. V and Ryan, J M The Graham Steell murmur versus aortic regurgitation in rheumatic heart disease. Results of aortic valvulography. Am J Med. 31 71 1961
2. Runco, V and Booth, R W Basal diastolic murmurs, Am Heart J 65:697 1963.
3. Brest, A. M Udhoji, V and Likoff W A re-evaluation of the Graham Steell murmur New England J Med 263 1229 1960
4. Wang, Y and Ariz, M Graham Steell murmur in rheumatic heart disease, Circulation 26 799 1962
5. Steell, G. The murmur of high pressure in the pulmonary artery Med. Chronicle 9:182, 1888
6. Dack, S Bleifer S Grishman, A and Donoso, E. Mitral stenosis auscultatory and phonocardiographic findings, Am. J Cardiol 5:815 1960.
7. Cohn, K. E., and Hultgren, H. N The Graham Steell murmur re-evaluated, New England J Med. 274:486, 1966.
8. Sobol, B. J Bottex, G Emirgil, C. and Gissen, H. Valvular insufficiency occurring during cardiac catheterization, Am. J Cardiol. 14:633 1964.
9. Collins, P Braunwald, E., and Morrow A. G Detection of pulmonic and tricuspid valvular regurgitation by means of indicator solutions, Circulation 20:561 1959
10. Brayshaw J R., and Perloff J K Congenital pulmonary insufficiency complicating idiopathic dilatation of the pulmonary artery Am. J Cardiol. 10:282, 1962.
11. Levin H S Runco, V Wooley C F and Ryan J M Pulmonic regurgitation following staphylococcal endocarditis an intracardiac phonocardiographic study Circulation 30:411 1964.
12. Soulie, P Baculard, P Bouchard, F Cornu, C., Laurens, P and Wolff F Le catheterisme du coeur au Micromanometre Arch. mal. coeur 54 Ann Suppl 1 1961
13. Luisada, A. A From auscultation to phonocardiography St. Louis, 1965 The C V Mosby Company p. 253.

Hemodynamic findings in children with endocardial fibroelastosis

Analysis of 22 cases

Thomas G. McLoughlin, M.D.
Gerold L. Schiebler, M.D.
L. Jerome Krovetz, M.D., Ph.D.
Gainesville, Fla.

Results of right heart catheterization in children with endocardial fibroelastosis (EFE) have been reported by several authors. The most constant findings were moderate elevations of pulmonary artery and pulmonary capillary wedge pressures and normal or slight elevation in right atrial pressure. Three of the authors[2,3,7] found no significant elevation of pulmonary artery pressures. Vestermark[8] reported systolic pressures in the right ventricle greater than 30 mm. Hg in nine of ten cases. All of his cases have died and the clinical diagnosis was confirmed in all seven necropsied.

Cardiac outputs were within normal limits in a total of 16 reported cases.[1] Mean values for stroke volume were normal in 14 cases reported by Moller and associates[1] and in one case reported by Miller and co-workers.

Left heart catheterization data have been reported in only eight patients.[2,4] The most consistent finding in these cases was an increase in left ventricular end-diastolic pressure with an average recording of 22 mm. Hg.

This paper presents an analysis of the findings obtained from right and left heart catheterizations and angiocardiography in a group of children fulfilling certain antemortem criteria for the diagnosis of primary EFE. While a positive diagnosis of EFE is possible only at necropsy, we feel that the clinical and hemodynamic picture presented in these children strongly suggest this diagnosis. As support for this contention, three patients who have died and come to necropsy have had the clinical diagnosis confirmed. The surviving patients cannot be distinguished from the necropsy cases by clinical, hemodynamic, or angiocardiographic methods.

This study was prompted by observation that a large number of children with the clinical diagnosis of EFE were responding well to digitalis therapy. Therefore, it was considered advisable to obtain baseline hemodynamic and angiographic data so

From the Department of Pediatrics, the Cardiovascular Laboratory, and the Clinical Research Center, J. Hillis Miller Health Center, College of Medicine, University of Fla., Gainesville, Fla.

Supported in part by the Fla. Heart Association, NIH Developmental Physiology Training Program (T1-HD-0094), Cardiovascular Training Grant (2-T1-HE-5493-04 (R1)), and Clinical Research Grant (FR-82). Dr. Krovetz is the recipient of a Research Career Development Award (1K3-9781-02).
Received for publication April 17, 1967.

that by serial study one might learn the natural history of this entity.

Materials and methods

The total of 22 children ranging in age from one month to eight years fulfilled the clinical and laboratory antemortem criteria for the diagnosis of EFE[3] (Table I). All were studied by right heart catheterization and 15 had additional left heart catheterization. At the time of these studies, 19 children were receiving digitalis and in chronic congestive heart failure; two (patients 15 and 19) had no clinical evidence of heart failure but remained on digitalis, and in one child (patient 22) digitalis had been discontinued two years previously.

All patients were catheterized in a supine position. No premedication was given to infants under one year of age. Children over this age were given a single intramuscular dose of Demerol (1 mg. per kilogram), Phenergan (0.25 mg. per kilogram) and Thorazine (0.25 mg. per kilogram). Standard cardiac catheterization and angiocardiography were carried out using methods previously reported from this laboratory.[11]

Systemic blood flow was calculated from indicator dilution curves employing a single rapid right heart injection of indo-

Table I. Initial criteria for antemortem diagnosis in 22 cases of endocardial fibroelastosis

Clinical	*Roentgenograms*	*Electrocardiogram*	*Angiocardiography*	*Catheterization*
Congestive heart failure (22)	Marked cardiomegaly especially LV and LA (21)	LVH (19) with LVSO pattern (17)	Large LV (17 of 20) and LA (13 of 14)	Various degrees of left heart failure (13)
No murmur (6), non diagnostic 1 2/6 systolic murmur (13), mitral insufficiency murmur (3)	Pulmonary venous congestion (17)	BVH in chronic cases (3)	Mitral insufficiency (14 of 21)	Elevated pulmonary artery systolic pressure > 35 mm. Hg secondary to No. 1 (10 of 21)
No clinical or laboratory findings of rheumatic carditis, glycogen storage disease, or myocarditis (22)		LAE (13)	Increase in LV wall thickness (16 of 21)	No intra- or extracardiac shunts (22), no left (15 of 15) or right (21 of 21) semilunar valve stenosis
		No evidence of anterolateral myocardial infarction (22)	Relatively little change in LV size during systole and diastole (14 of 21)	Normal systemic artery pressures (22)
			Normal origin of coronary arteries (20 of 20)	Below normal range for LV dp/dt (4 of 14)
			No aortic stenosis, ductus, or coarctation (21 of 21)	

Key: LV, left ventricle; LA, left atrium; LVH, left ventricular hypertrophy; LVSO, left ventricular systolic overload; LAE, left atrial enlargement; BVH, biventricular hypertrophy; dp/dt, first derivative of pressure pulses.
Numbers in parentheses refer to cases fulfilling criteria.

Table II Endocardial fibroelastosis

Case	Age (mo)	Sex	Ht (cm)	Wt (kg)	Heart rate	A-V Dif	SBF (L/m)	RA mean	Rt ventricle E D	Rt ventricle dp/dt	Pulm artery mean	LA M	Lt ventricle E-D	Lt ventricle dp/dt	Sys A mean
1	1	F	47	2 4	170	51	0 62	−5	8	1 918	30	4	—	—	54
2	2	F	60	5 4	110	45	0 90	15	2	644	35	23	30	1 660	68
3	2	M	60	4 5	148	71	1 14	6	6	830	45	—	—	—	60
4	3	M	56	4 2	125	65	0 55	8	6	678	18	8	8	1 690	92
5	4	F	64	5 6	102	75	1 6	2	3	400	14	5	9	1 590	66
6	5	F	70	8 1	140	71	0 86	2	5	370	17	7	12	1 150	55
7	7	F	64	5 4	140	42	1 66	7	11	416	27	20*	10	1 660	70
8	7	M	70	7 1	140	69	2 48	6	10	550	30	13	23	1 370	80
9	8	M	62	5 0	140	50	1 03	10	11	252	—	13	—	—	80
10	13	F	73	8 9	140	41	1 27	3	5	160	16	10	10	1 080	61
11	15	F	69	7 7	120	65	2 01	8	14	932	59	—	22	1 070	79
12	17	M	77	9 2	150	—	2 94	5	22	1 020	32	17	—	—	60
13	18	M	84	10 8	150	47	2 64	8	4	480	19	9*	7	—	69
14	18	M	79	9 0	105	56	1 54	1	2	270	10	—	8	930	51
15	1	M	84	10 5	84	45	1 78	3	3	286	8	9	5	1 300	73
16	22	M	79	8 3	150	—	3 06	4	5	608	20	10	—	—	71
17	30	F	83	9 6	120	49	—	—	3	654	16	8	10	1 800	81
18	31	F	86	11 7	110	33	2 24	6	7	410	26	10	9	1 485	74
19	35	M	97	16 3	100	43	2 72	3	7	252	14	7	—	—	72
20	30	M	82	13 4	120	54	1 58	4	7	324	16	8	—	—	61
21	60	M	112	19 2	79	51	2 30	9	12	740	30	21	24	1 480	90
†	84	M	122	22 6	90	81	1 11	9	15	490	—	—	27	1 100	69
22	96	M	136	28 4	97	46	5 65	6	5	640	16	9*	5	1 800	80

Key A-V Dif arteriovenous difference in volumes per liter SBF systemic blood flow RA, right atrium Rt, right E D end diastolic pressure in mm Hg dp dt first derivative of ventricular pressure pulse Pulm, pulmonary LA, left atrium Lt, left Sys A systemic artery M mean pressure mm Hg

*Pulmonary artery capillary pressure

†Repeat study of case at 2 ___ interval

cyanine green with systemic arterial sampling The densitometer employed a Waters XC 250 was calibrated with known dye concentrations mixed with the subjects heparinized arterial blood Dye concentrations were measured at 0 5 or 0 1 second intervals, using a semiautomatic analogue to-digital converter (Gerber oscillogram amplitude tabulator*) Cardiac outputs were calculated by the Stewart Hamilton method using an IBM 09 1401 computing system[13]

Arteriovenous differences of oxygen expressed in volumes per liter were measured in blood samples withdrawn simultaneously from the main pulmonary artery and a systemic arterial sampling site Oxygen saturations and arterial blood oxygen binding capacities were determined by the Van Slyke-Neill method

*Gerber Scientific Instrument Company Hartford, Conn.

Vascular resistances were calculated according to the following formula

Systemic resistance = (mean systemic arterial pressure − mean right atrial pressure) / (cardiac output).

Total pulmonary resistance = (mean pulmonary artery pressure) / (cardiac output).

Pulmonary arteriolar resistance = (mean pulmonary artery pressure − mean left atrial pressure) / (cardiac output).

The results of these calculations are given in peripheral resistance units (p r u) the units of which are millimeters of mercury per liter per minute.

Stroke volume was calculated by dividing cardiac output by heart rate Left ventricular stroke work was calculated as stroke volume × mean systemic artery pressure minus left ventricular end-diastolic pressure × 1334 + 10^7 the units of which are Newton meters

First derivatives of right and left ven

Table III *Endocardial fibroelastosis*

Case	Stroke volume (c.c.)	Left ventricular stroke work (Newton-meters)	Systemic resistance (mm. Hg/L./min.)	Total pulmonary resistance (mm. Hg/L./min.)	Pulmonary arteriole resistance (mm. Hg/L./min.)
1	3 6	—	95	48	41 9
2	8 2	0 04	58	39	13 3
3	7 7	—	47	39	—
4	4 4	0 05	152	33	18 2
5	15 7	0 12	40	9	5 6
6	6 1	0 04	61	20	11 6
7	11 9	0 09	38	16	4 2
8	17 7	0 13	29	12	6 9
9	7 4	—	65	—	—
10	9 1	0 06	44	13	4 7
11	16 7	0 13	35	29	—
12	19 6	—	18	11	5 1
13	17 6	0 14	23	7	3 8
14	14 7	0 08	32	6	—
15	21 2	0 19	39	4	0 6
16	20 4	—	21	6	3 3
17	—	—	—	—	—
18	20 4	0 18	30	11	7 1
19	27 2	—	24	5	2 6
20	13 2	—	36	10	5 1
21	29 1	0 26	35	13	3 9
	12 3	0 07	54	—	—
22	58 2	0 58	13	3	1 2

*Repeat study of case 21 at ... year interval

tricular pressures (dp dt) were obtained by measuring the maximum slopes of at least five pressure cycles. Paper speeds were 100 or 200 mm per second with 0 1 second time lines. Since our method utilized conventional pressure recording techniques which are limited to a maximum of about 20 cycles per second (c.p.s.) our values differ from those using a faster responding catheter tip micromanometer. Because of the variation in technique the values obtained are sufficiently different and not interchangeable. However using the same method in normal children[13] and those with EFE the values for dp/dt are considered valid although relative.

Selective left ventricular or pulmonary artery angiocardiograms, employing a biplane roll-film changer at 6 frames per second (f.p.s.) or a 16 mm cinefilm at 60 f.p.s. were used to estimate the left ventricular cavity and wall size, left ventricular contractility and the presence or absence of mitral insufficiency. Retrograde aortography was used to demonstrate the origin of the coronary arteries.

Data obtained from the cardiac catheterization was transferred to IBM cards and calculations performed using BIOMED computer programs from UCLA.[14] Stepwise multiple linear regression analyses (BIOMED) were calculated from data obtained in normal children in the same laboratory.[13] These data were used as the standard when comparing the hemodynamic status of patients with EFE.

Results

Systemic output, stroke volume and stroke work (Tables II and III).

Systemic and pulmonary blood flow were considered equal in the absence of any demonstrable left-to-right or right-to-left shunt. The indicator dilution technique was used in all cases to exclude such shunts. The results shown in Fig. 1 are expressed as per cent variation from the predicted normal values. The normal range is ex

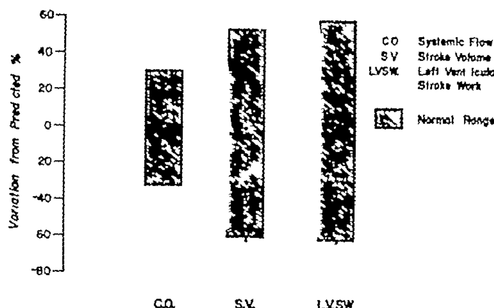


Fig 1 Cardiac output, stroke volume, and stroke work expressed in per cent variation from the predicted normal.

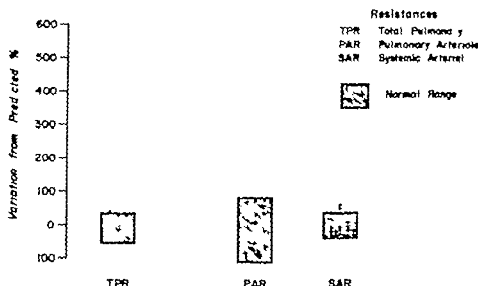


Fig 2 Calculated systemic artery pulmonary artery and pulmonary arteriolar resistances expressed in per cent variation from the predicted normal.

pressed in plus or minus two standard deviations from the predicted normal mean. Systemic blood flow was below two standard deviations in six of 22 measurements but the stroke volume was low in only two of the 22 studied Values for left ventricular stroke work were two standard deviations below the normal in five of 15 cases (Fig 1)

Mean pulmonary artery pressure

Mean pulmonary artery pressure was above normal (> 22 mm Hg) in nine of 21 cases (Table II) The variability of pulmonary artery pressures in this series

is probably a reflection of the varying degree of left heart failure

Ventricular end-diastolic pressure

Right and left ventricular end-diastolic pressures are tabulated in (Table II). In six of 22 cases the RVED* pressure was elevated above the upper limits of normal (8 mm. Hg). LVED† pressure was above the upper limits of normal (12 mm. Hg) in four of 15 cases. Although cases of EFE have had right atrial and right ventricular pressure curves simulating constrictive pericarditis[3] they were not a feature of this study. The elevation of right atrial and right ventricular end-diastolic pressures in some of our patients may be considered as secondary to severe heart failure.

Calculated vascular resistances

Systemic artery resistances (Fig. 2) were within the normal range in all but three patients. Both total pulmonary and pulmonary arteriolar resistances were increased in slightly more than half the cases (Fig. 2).

First derivative of ventricular pressure pulses (dp/dt)

Values of dp/dt expressed as millimeters of mercury per second for right and left ventricular pressure curves are tabulated in Table II. All 14 LV dp/dt values were below the mean normal value (2,178 mm. Hg per second) while four were more than two standard deviations below the normal mean. Right ventricular dp/dt values were above the mean normal value (360 mm. Hg per second) in 70 per cent of the cases in this report, consistent with elevation of right ventricular pressures.[17]

Angiographic measurement of left ventricular cavity and wall size

To measure the left ventricular cavity and wall, we used the method described by Levine, Rockoff and Braunwald[14] (Fig. 3). This simplified technique is fast and quick enough that it can be carried out routinely. Values for left ventricular cavity size and wall thickness are shown in Table IV. Sixteen of 22 measurements of left ventricular cavity and wall size were more than two standard deviations above the predicted normal (Fig. 4).

*RVED = right ventricular end-diastolic.
†LVED = left ventricular end-diastolic.

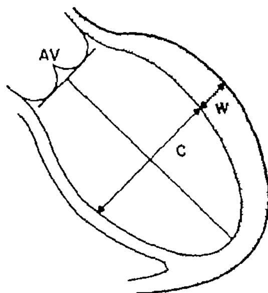


Fig. 3. Schematic method for measuring size of the left ventricular cavity and wall thickness. In the anteroposterior view, a perpendicular line is drawn from the center of the aortic valve (AV) to the apex. This line is bisected and the diameter of the contrast filled cavity (C) is measured in diastole. The outer nonopacified portion is equivalent to the wall (W) thickness. The values are recorded in centimeters.

Angiocardiographic evaluation of left ventricular contraction

The left ventricle was considered to contract poorly, i.e., there was little change in visible volume size between systole and diastole in 14 of 21 cases studied.

Angiocardiographic evidence for mitral insufficiency

Mitral insufficiency was present in 11 of 14 selective left ventricular injections and in three of six selective pulmonary artery injections.

Retrograde aortography

There was normal origin of both coronary arteries as demonstrated by root of aorta angiograms in all 20 cases in which this study was performed. Aortography was not performed in one case and in the remaining case a selective left ventricular angiogram visualized a normal coronary artery pattern.

Discussion

For complete substantiation of the diagnosis of EFE, it is obviously necessary to

Table IV Summary of angiocardiography

Case	Left ventricular size: Cavity (mm.)	Left ventricular size: Wall (mm.)	Left ventricular contractility	Mitral insufficiency
1	45	15	Poor	N
2	82	14	Poor	Yes
3	70	15	Poor	Yes
4	61	15	Poor	Yes
5	40	10	Poor	Yes
6	65	10	Poor	Yes
7	86	15	Normal	Yes
8	72	13	Poor	N
9	40	13	Normal	Yes
10	94	16	Poor	N
11	103	38	Poor	Yes
12	70	5	Normal	N
13	93	15	Poor	Yes
14	89	16	Poor	N
15	40	15	Normal	No
16	—	—	—	—
17	53	12	Normal	Yes
18	65	8	Poor	Yes
19	56	10	Normal	Yes
20	86	15	Poor	Yes
21	90	16	Poor	Yes
	105	13	Poor	Yes
2	115	12	Normal	N

*Repe... ars

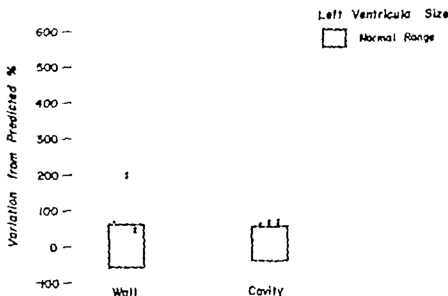


Fig. 4 Left ventricular ity size and wall thickness expressed per cent variation from the predicted normal.

have necropsy confirmation. If, however, we are to obtain physiologic information during the course of the disease process, a certain amount of diagnostic uncertainty is unavoidable. All the patients reported here had one or more bouts of congestive heart failure, no significant murmurs or a murmur of mitral regurgitation, and left ventricular enlargement. In addition, the presence of rheumatic fever, anomalous left coronary artery, glycogenosis of the heart, or myocarditis was not present by clinical or laboratory examination.

A clinical summary of the children who died and the survival group are shown in Tables V and VI. The absence of necropsy confirmation in the survival group may make one hesitate to label these children as having EFE. However, in the surviving group the clinical, hemodynamic, and angiocardiographic findings are indistinguishable from those in the children who had necropsy confirmation. The surviving group may have an endomyocardial disease indistinguishable from EFE.

At cardiac catheterization, the variable

Table V. Summary of patients who died

Case No.	Age onset CHF (mo.)	Age at cardiac catheterization (mo.)	Duration digital therapy (mo.)	Age at death (mo.)	Necropsy
1	1	1	1½	2½	EFE
3	2	2	8	10	EFE and MI
4	3	3	2	5	Refused
7	7	7	12	19	EFE and MI

Key: CHF, congestive heart failure; EFE, endocardial fibroelastosis of the left ventricle; MI, mitral insufficiency.

Table VI. Summary of surviving patients

Case No.	Age onset CHF (mo.)	Age at cardiac catheterization (mo.)	Age last follow-up (yr.)	Digitalis therapy: Administered	Digitalis therapy: Duration	Present cardiac status
2	2	2	4	+	3 yr.	Asymptomatic
5	4	4	1	+	1 yr.	Stable
6	3	5	¾	+	6 mo.	Stable
8	7	7	1	+	6 mo.	Stable
9	8	8	4	+	3 yr.	Stable
10	13	13	3	+	2 yr.	Stable
11	3	15	4	+	3 yr.	Asymptomatic
12	17	17	Lost	+		
13	15	18	2	+	1	Stable
14	18	18	2	+	1	Stable
15	14	21	3	+	2 yr.	Asymptomatic
16	22	22	6	−	3 yr.	Asymptomatic
17	24	30	Lost	+		?
18	30	31	5	+	2 yr.	Stable
19	3	35	6	−	3 yr.	Asymptomatic
20	30	30	6	−	3 yr.	Asymptomatic
21	60	60	8	+	3	Chronic CHF
22	40	96	10	−	4 yr.	Asymptomatic

Although these children show no overt symptoms, they all have some degree of residual left ventricular enlargement by serial x-ray and electrocardiograms.

degree of elevation of right heart systolic and right and left heart end-diastolic pressures is a reflection of the severity of heart failure and the variation in response to digitalis therapy. Systemic flow was within a normal range in 75 per cent of our cases. Underestimation of systemic output by indicator dilution curve technique in the presence of mitral regurgitation has been estimated by Rahimtoola and Swan[14] to be approximately 20 per cent. However, a more recent study[15] has shown that even severe mitral regurgitation does not vitiate indicator dilution determination of systemic output after right heart injection and systemic arterial sampling if the down slope of the primary dilution curve permits a straight line semilogarithmic extrapolation. In only one case (21) a repeat study were we not able to obtain an accurate semilogarithmic extrapolation.

Stroke volume was decreased in only two of 22 children. This is not surprising since a dilated left ventricle can apparently maintain a reasonably normal stroke volume with minimal volume change between systole and diastole.[16] Left ventricular stroke work was below normal in one third of our cases. The measurement may reflect a degree of functional myocardial impairment whatever the etiology. In our experience the left ventricular stroke work may be normal at rest in children with EFE but becomes abnormal under stress, e.g., by increasing systemic arterial resistance.[n] The simultaneous elevation of the calculated total pulmonary artery and pulmonary arteriolar resistance obtained in our present study cannot be explained on the basis of left heart failure alone. The elevation of pulmonary arteriolar resistance may be secondary to variable degrees of vasoconstriction of the pulmonary arterioles.

In addition to the usual data obtained by right and left heart catheterization, measurement of peak first derivative of ventricular pressure pulses was carried out in the present study. Four of the 14 LV pressure tracings had dp/dt values two standard deviations below the normal predicted mean and all were below the normal mean value. Values for left ventricular dp/dt in EFE have been reported by Miller and co-workers[4] in three cases, two of whom had associated coarctations of the thoracic aorta. All three had values below their normal control group. Poor contractility of the myocardium on any basis may theoretically produce a subnormal dp/dt value.[17]

Measurements of wall thickness and cavity size of the left ventricle in cases of EFE have not previously been reported. Measurement on angiocardiographic films of left ventricular wall thickness and cavity size is a valuable technique. Although the simple method employed is subject to errors in using the same technique in cases of EFE and normals it furnished a reasonable comparison. The low values for left ventricular cavity (c)/wall (w) ratio in EFE, despite a dilated ventricle is produced by a proportionately greater wall thickness relative to increase in cavity size.

In five left heart anomalies in children the lowest left ventricular cavity/wall ratio was found in idiopathic hypertrophic subaortic stenosis (IHSS) followed by EFE and aortic valvar stenosis (AS) (Fig. 5). IHSS and AS can be readily distinguished from EFE by other means. Since mitral insufficiency is a frequent accompaniment of EFE and indeed some authors consider this an integral part of the fibroelastotic process, congenital mitral insufficiency and idiopathic myocardial hypertrophy (IMH) must be considered in the differential diagnosis of EFE. Left ventricular cavity size and wall thickness were measured in one child and five young adults diagnosed by catheterization and angiocardiography as having IMH. The ratio of c/w was normal in half the cases and differed significantly ($p < 0.05$) from cases of EFE. Two children with isolated congenital mitral insufficiency, one proved at necropsy, showed normal c/w ratios. Thus this relatively simple measurement appears to be of value in the differential diagnosis of EFE.

Estimation of the degree of contractility of the left ventricle by comparing volume size between systole and diastole is a valuable though not a completely diagnostic aid in cases of EFE.[1,4] One case proved at necropsy in our study (case 7) had reasonably normal volume changes by angiocardiography. Fourteen of 21 children in our present study had little volume change

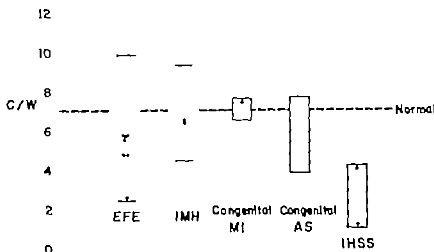


Fig. 5. Ratio of left ventricular cavity (C) to wall (W) thickness (C/W) in selected left heart anomalies.

between systole and diastole and this finding adds support to their diagnosis of EFE.

Emphasis has been placed on the occurrence of mitral insufficiency in children with EFE by Moller and associates. Fourteen of 21 children in our study had some degree of mitral insufficiency at the time of angiocardiography. Of these fourteen one died but no necropsy was performed and two others had gross evidence of mitral insufficiency at necropsy. The presence of mitral insufficiency would thus appear to support the diagnosis of EFE, although its presence is not diagnostic.

Cardiac catheterization and angiocardiography in children who fulfill the clinical criteria for EFE are important, not only to rule out specific cardiac anomalies, but also to gain some knowledge of the natural history of this entity. Seven of the children in this report who presented both early and later in life with congestive failure are now asymptomatic (Table VI). In three of these same seven cases, serial x-rays and ECG(s) have shown continued resolution of the initial left ventricular enlargement. Similar cases with a clinical diagnosis of EFE have been reported to respond to digitalis and become asymptomatic in varying periods of time.[21] Twelve additional children are considered stable on follow-up examinations in that their chronic heart failure is managed by digitalis therapy. Two children have been lost to follow-up. In contrast, case 21 in this series, studied a second time after a two-year interval, showed further hemodynamic deterioration as manifested by decreases in systemic output, stroke volume, stroke work, and LV dp/dt.

Summary

Cardiac catheterization and angiocardiography results were recorded and analyzed in 22 children fulfilling our antemortem criteria for the diagnosis of EFE. There were varying degrees of left and right heart failure. Systemic output and stroke volume were normal in the majority of cases despite relatively poor left ventricular contractility evidenced by low LV dp/dt values as well as by angiocardiography. Left ventricular stroke work at rest was decreased in one third of the cases reflecting functional myocardial impairment. Left ventricular cavity and wall size were increased in 75 per cent of our cases. Calculation of cavity/wall ratios is of value in differential diagnosis of left heart anomalies. Fourteen of 21 cases had angiocardiographic evidence for poor left ventricular contractility and mitral insufficiency.

With necropsy confirmation in only three of 22 cases, the establishment of certain antemortem criteria for the diagnosis of EFE, even though not conclusive

was mandatory in the selection of cases. The natural course of this clinical entity remains to be elucidated

The authors wish t thank the contributors t the W lter Parrish Memorial Fund for their financial assistance during this tudy

REFERENCES

1 Moller J H Lucas, R V J Adams, P J Anderson, R C Jorgens, J and Edwards, J E. Endocardial fibroelastosis. A clinical and natomic study of 47 patients with emphasis on its relationship to mitral insufficiency Circulation 30 759 1964
2. Adams, F H nd Katz, B E Endocardial fibroelastosis, J Pediat 41 141 1952
3. Linde, L M Adams, F H and O Loughlin B. J Endocardial fibroelastosis. Angiocardiographic tudies, Circulation 17:40, 1958
4 Ly field J Gasul, B M Luan, L L and Dillon, R. F Right and left heart catheterization and angiocardiographic findings in idiopathic cardiac hypertroph with endocardial fibroelastosis, Circulation 21:386 1960.
5 Lambert E. C nd Vlad, P Primary endomyocardial disease Pediat. Clin North America 5 1057 1958
6. Miller G A H Rahimtoola, S H Ongley P A and Sw n, H J C. Left ventricular olume and volume change in endocardial fibroelastosis Am J Cardiol 15:631 1965
7 Graham, G. R. Cardiomyopathies. CIBA Foundation symposium Boston, 1964 Little Brow & Cor pan p 353
8 Nadas, A S Pediatric cardiology ed 2, Philadelphia, 1963 W B Saunders Company p 270
9 Vestermark, S Primary endocardial fibrolastosis, Cardiologia 18:520, 1966.
10. M Loughlin, T G Schiebler G L, and Krovetz, L J Endocardial fibroelastosis in American Negro children A distinct entity? Am Heart J 1 748 1966
11 Krovetz, L J Lormez, A. E. and Schiebler G L Cardiovasc lar manifestations of the Hurler yndrome. Hemodynamic nd ngiocardiographic observations n 15 patients, Circulation 31 132, 1965
12. Krovetz, L J Crowe, W F Fairchild B T Grumbar P and Mitchell, B A tomated computation of cardiac output from indicator dilution curves. In preparation.
13. Krovetz, L J McLoughlin, T G Mitchell, B and Schiebler G. L. Hemodynamic findings in normal children, Pediat. Res. 1 122 1967
14 Levine, N D Rockoff S. D and Braunwald, E. An angiocardiogr phic analysis of the thickness of the left ventricular wall and cavity in aortic tenosis and other valvular lesions, Circulation 28:339 1963
15 Dixon, W J editor (1964) BMD Biomedical Computer Program Health Sciences Compt ing Facility U versity of California, Los Angeles
16 Yu, P N Cohen, J Schreiner B F J and Murphy G W Hemodynamic alterations in primary myocardial disease, Progr Cardiovas. Dis 7 131 1964
17 Gleason, W L, and Braun ald, E. Studies on the first derivative of the ventricular pressur pulse in man, J Clin. Invest. 41:80, 1962
18. Rahimtoola, S. H and Swan, H. J C. Calculation of cardiac output f om indicator dilution curves in the presence of mitral regurgitation, Circulation 31 711 1965
19 Samet, P Bernstein, W H and Castillo, C. Validity of indicator-dil tion determinations of cardiac output in patient with m tral regurgitation Circulation 33:410, 1966
20. Black Schaffer B Inf tile endocardial fibroelastosis, Arch. Path. 63:281 1957
21 Krovetz, L J M Loughlin T G nd Schiebler G. L. Studies of left ventricular function in children by increasing peripheral resistance with angiotensin. Presented t the Society for Pediatric Research, 37th Annual meeting Atlantic City N J April 28-29 1967 (p. 15)
22 Keith J D Rowe, R. D and Vlad, P Heart disease in infancy and childhood, ed. 2 New York, 1967 The Macmilla Company p. 872

Problems in the hemodynamic diagnosis of tricuspid insufficiency

Kenneth B Cairns M.D
Frank E. Kloster M.D **
J David Bristow M.D ***
Martin H Lees M.D ****
Herbert E. Griswold M.D *****
Portland Ore

Deformity of the tricuspid valve usually is found in association with rheumatic disease of other valves.[1] Tricuspid insufficiency (TI) commonly accompanies stenosis, but also occurs with right ventricular failure and dilatation then being termed functional. Clinical evaluation of TI has long been attempted primarily on the basis of physical findings and right atrial or jugular venous pressure levels and contours The presence of physical signs of TI however usually reflects gross regurgitation and findings are often equivocal with less severe disease Moreover there are suggestions that the right atrial pressure levels and contour do not have the significance often attributed to them Although our diagnostic capabilities are thus limited the current interest in tricuspid valve surgery necessitates optimal understanding of tricuspid disease.

Angiocardiography has been useful in assessing insufficiency of other valves, but the procedure itself has been reported to cause tricuspid regurgitation in dogs.[11] We evaluated the tricuspid valve with right ventricular angiocardiography (RVA) in 141 children and adults with congenital or rheumatic heart disease The angiocardiographic results, where possible were compared with the findings by valve palpation at the time of cardiac surgery We learned that we could not conclusively prove the existence of TI by the regurgitation of contrast agent to the right atrium apparently because of interference with valve function by the catheter However we could exclude TI by the absence of angiographically demonstrable regurgitation Observations were then made in patients proved by RVA not to have TI and in those proved at surgery to have it regarding the significance of right atrial

From the Department of Pediatrics and the Division of Cardiology Department of Medicine University of Oregon Medical School Portland, Ore
Supported by United States Public Health Service Program Project Grant H [illegible]
Received for publication March 20, 196[illegible]
*Fellow in Cardiology University of Oregon Medical School, Portland, Ore Address Division of Cardiology University of Oregon Medical School, Portland, Ore 97201
** Assistant Professor of Medicine University of Oregon Medical School, Portland, Ore
*** Associate Professor of Medicine and Director Cardiology Laboratory University of Oregon Medical School Portland Ore
**** Associate Professor of Pediatrics, University of Oregon Medical School, Portland, Ore
***** Professor of Medicine and Head, Division of Cardiology University of Oregon Medical School, Portland, Ore

pressure level and contour in TI and the roles of atrial fibrillation ventricular premature contractions, and right ventricular failure in its causation

Methods

Right ventricular cineangiocardiograms from 141 adults and children with congenital and rheumatic heart disease were reviewed Each of the observers independently graded a film positive for TI if he saw any contrast in the right atrium during or immediately following injection into the right ventricle The film was judged positive if so graded by at least two observers. If there was an obvious cause for false positive regurgitation such as multiple premature beats or the catheter tip very near the tricuspid valve the cineangiocardiogram was excluded from further consideration The charts were reviewed for clinical evidence of TI electrocardiograms (ECG) were inspected right heart pressures during several respiratory cycles were analyzed and the surgical description of the tricuspid valve was noted in operated cases. The surgical criterion for TI was the presence of any regurgitant flow detected by a finger held in the right atrium (RA) above the tricuspid valve Although it is possible that TI could have been present at the time of catheterization but not at the time of surgery or vice versa this seemed the best available validation of the results of RVA In all instances, vigorous attempts had been made to achieve the best possible state of cardiac compensation both for catheterization and operation

Cineangiocardiography on 16 mm film at 60 frames per second was performed with power injection of 80 per cent sodium iothalamate through a right ventricular catheter introduced from the right arm in adults, or the saphenous or femoral vein in children No 6 or 7F catheters with closed end and multiple side holes were used The average amount of contrast material injected wa 0.5 mL per kilogram at an average injection pressure of 350 p.s.i The catheter tip was usually placed in the right ventricular outflow tract Pressures were recorded by Statham P23Gb and P23Db strain gauges and a Sanborn photographic recorder

Angiocontin Mallinckrodt Pharmaceuticals.

Results

Right ventricular angiocardiography In 46 patients over 10 years of age RVA was negative for TI in 27 and positive in 13 Six cases were excluded due to obvious multiple ventricular premature contractions (VPC's) or a catheter tip very close to the tricuspid valve Of the 27 with negative RVA the valve was subsequently palpated during open heart operation in six and none had TI Of the 13 with positive RVA eight were operated upon for disease of other valves. Seven of the eight were found to have TI and one did not. The five nonsurgical patients with positive RVA include two with firm clinical evidence for TI and three without such evidence Thus, in patients over 10 years of age there were no false negatives for TI in the six of 27 patients with negative RVA who were operated upon Of 13 cases with positive RVA one of eight coming to surgery was a proved false positive and a total of four could be false positives

Of 95 patients 10 years of age and younger with congenital heart disease but in whom there was no reason to suspect tricuspid valve disease, RVA was positive for TI in 18 and negative in 77 Thus in 20 per cent of a large group of infants and children with a catheter from a saphenous or femoral vein across the tricuspid valve some regurgitation was seen with selective angiocardiography

In 22 of the cases over age 10 the ECG's recorded during the injection were available for review In 14 of these no regurgitation was seen on angiocardiography although 12 had VPC's during injection and 6 of the 12 had multiple VPC's. The eight angiocardiograms showing regurgitation were accompanied by VPC's in six instances. It was clear that many injections caused multiple VPC's but multiple VPC's did not always cause TI

We chose the previously mentioned surgical criterion as proof of TI feeling that RVA might give too many false positives to allow its use in establishing this diagnosis. In view of the sensitivity of angiocardiography and because we found no false negatives we felt confident in con

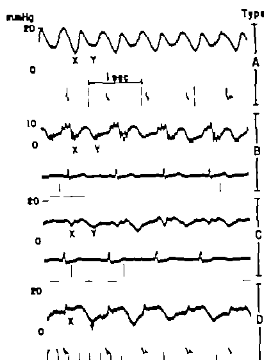


Fig. 1. Right atrial pressure contours, as described in text. *A*, The X descent is deeper than the Y. *B*, X is equal to Y. *C*, X is slightly shallower than Y. *D*, the X descent is barely existent, the C wave leading almost directly into a large regurgitant systolic wave. In this illustration, Types *A* and *B* were associated with sinus rhythm and *C* and *D* with atrial fibrillation.

sidering our patients with negative RVA to have reasonable proof of the absence of TI. By these criteria, we then had 34 patients with validation of TI or its absence. A total of 27 of these were proved negative by RVA and will be referred to as "RVA negative" cases. Seven were proved positive by operation and will be called "surgical positive" cases. These were evaluated with regard to differences in heart rhythm and right atrial pressure levels and contour.

Cardiac rhythm. Eight patients of the 27 who were "RVA negative" for TI had atrial fibrillation. Of the seven "surgical positive" cases, five had atrial fibrillation. Four of these five had marked tricuspid valvular deformity and the remaining one had severe right ventricular failure and dilatation. Thus atrial fibrillation was commonly seen without associated TI. TI was not associated with fibrillation in the absence of intrinsic tricuspid disease or right heart failure.

Right atrial pressure. The pressure contours were grouped into four different types as shown in Fig. 1: (1) X deeper than the trough of the Y descent (type A), (2) X = Y (type B), (3) X slightly shallower than Y (type C), and (4) X at least 3 mm. Hg shallower (almost absent)

Table I. Distribution of right atrial pressure types

	Right atrial pressure pattern							
	X deeper than Y (type A)		*X = Y (type B)*		*X slightly shallower (type C)*		*X nearly absent (type D)*	
	SR	*AF*	*SR*	*AF*	*SR*	*AF*	*SR*	*AF*
Present study: 34 cases with known tricuspid valve condition								
TI	2	0	0	0	0	0	0	5
No TI	18	0	1	3	0	5	0	0
100 cases of rheumatic or congenital heart disease randomly selected from files	47	1	15	3	*SR* 7†		*AF* 27	

*SR, sinus rhythm; AF, atrial fibrillation; TI, tricuspid insufficiency.

†In the 100 cases from the files, it was desired to know only the relationship of rhythm to the relative depths of X and Y. Therefore, types C and D, both having X less deep than Y, were not distinguished.



Fig 2 A patient with proved tricuspid valve deformity and marked tricuspid insufficiency There is sinus rhythm and the X descent is deeper than the Y

with the A or C wave leading almost directly into a large V wave (type D)

A commonly used criterion for the diagnosis of TI has been a right atrial (RA) pressure contour of types B C or D with the trough of the X equal to or deeper than X [13] Type A with X deeper than Y should connote normal valve function As shown in Table I our 20 patients with type A contours all had sinus rhythm and two had surgically proved TI (see Fig 2) Of the nine with type B or C contours, eight had atrial fibrillation and all nine were shown by RVA not to have TI Thus, X deeper than Y did not exclude TI but in fact correlated better with sinus rhythm than with tricuspid competence An X equal to or slightly shallower than Y (types B and C) did not prove the presence of TI and in fact correlated better with atrial fibrillation than with TI

To extend these observations regarding the effects of sinus rhythm and atrial fibrillation on the RA pressure pattern the RA pressure tracings of 100 patients with congenital or rheumatic heart disease were selected at random from our files and reviewed (see Table I) A total of 47 out of 48 type A curves were associated with sinus rhythm Of 31 cases with atrial fibrillation X was deeper than Y in just one X and Y being equal in three

The type D contour has been considered typical of a marked degree of TI [4] We found that in eight patients of whom five had surgically proved TI two had right ventricular *failure* but no proof of TI or of its absence and one was RVA negative for TI but had right ventricular failure with a right ventricular pressure of 48/9 The type D pattern then seems fairly specific for TI though there appear to be false positives with right heart failure Looked at from another aspect, five of seven surgically proved TI cases had type D right atrial pressure contour and all five of these had atrial fibrillation. The two cases of surgically proved TI without this pattern had normal sinus rhythm

In order to determine that the type D curve is not produced by atrial fibrillation alone the 13 patients with atrial fibrillation among our 34 proved (RVA negative or surgical positive) cases were analyzed Six of the 13 had this pattern Five of those had tricuspid insufficiency at operation and one was RVA negative but had right heart failure

As shown in Fig 3 mean RA pressure was highly variable in the patients without TI TI with high right atrial pressure was usually associated with atrial fibrillation.

Organic TI functional TI and right ventricular failure without TI The seven surgical-positive patients were divided into two groups. Four had grossly thickened valves and definite tricuspid stenosis found at operation while three had no valve deformity or so little that the TI would have to be assumed largely functional These groups, admittedly small could not be separated by the incidence of atrial fibrillation level of the mean RA pressure or the frequency of the type D right atrial pressure pattern

Ten patients RVA negative for TI had right ventricular end-diastolic pressures of 7 mm Hg or greater Eight of them had sinus rhythm their average RA mean

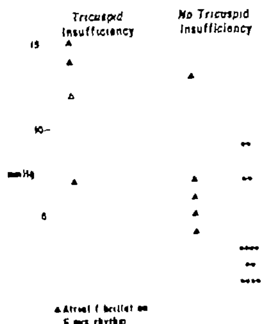


Fig. 3. Mean right atrial pressure levels at cardiac catheterization in seven patients who later were proved at operation to have tricuspid insufficiency and in 27 others with negative right ventricular angiocardiograms.

pressure being 7 mm. Hg compared with 11 mm. Hg in the two with atrial fibrillation. These pressure levels are similar to the RA mean pressure levels in our patients with TI with sinus rhythm and with fibrillation, respectively. RA pressure contours in the eight with sinus rhythm had X deeper than Y and in the two with fibrillation had X equal to or shallower than Y.

Tricuspid stenosis. Of the seven patients with surgically proved TI, six had abnormal valve cusps. In two of these there was only slight cusp thickening and no significant stenosis. No pressure gradient had been detected across the tricuspid valve at catheterization in these two. In four there was significant tricuspid stenosis. A diastolic pressure gradient was detected at preoperative cardiac catheterization in three and not in the fourth. These three had atrial fibrillation, the type D right atrial pressure pattern, and RA mean pressures of 7, 1 and 15. The fourth had sinus rhythm, a normal pressure contour, and a RA mean pressure of three.

Discussion

Although there are well known physical findings associated with tricuspid regurgitation, right atrial pressure data have been considered more sensitive. It has been stated that if the X descent is deeper than the Y, TI does not exist and if it is shallower, TI is present.[12,13] Müller and Shillingford attempted to validate these concepts. They studied 21 patients with clinical signs of tricuspid regurgitation and described the right atrial pulses. Four of the patients with severe disease later came to necropsy. In the majority of patients, and in all those with suspected moderate or mild disease, it was not possible to confirm anatomically the presence of tricuspid regurgitation and thus it was not possible to prove the significance of the atrial pressure curves. Notwithstanding the absence of proof of the significance of small changes in right atrial pulse contour, such changes or lack thereof have been used as evidence for certain specific points of view. For example, atrial fibrillation has been believed commonly associated with TI based largely on a contour of the RA pressure pulse considered typical.[13-4] In addition, it has recently been proposed that cor pulmonale is infrequently associated with TI, the evidence being that X was lower than the pressure just before atrial systole in the RA pressure tracings of the patients studied.[12] Mild elevations of RA pressure due to RV failure have been thought to be associated with TI because of abnormalities of the RA pressure configuration.

Rubeiz and associates[1] have challenged existing views. They studied six patients with sinus rhythm who had mitral stenosis and functional tricuspid regurgitation, proved by digital exploration of the valve. The X descent was well preserved in all, being deeper than the Y in five. There was no V wave exaggeration. At least three had right atrial mean pressures of less than 5 mm. Hg. They concluded that a normal right atrial pressure pattern (with X deeper than Y, our type A) does not exclude functional TI.

It seemed clear that other methods were needed for adequate tricuspid valve evaluation and clarification of the significance of RA pressure curves. Angiocardiography

is presently a widely accepted technique for the diagnosis of aortic and mitral incompetence. When a catheter traverses the valve, however, false positive regurgitation has been claimed frequent by some and infrequent by others.[4, 11] We are not aware of previous studies showing the frequency of false positive TI during RVA in man. We believe right ventricular cineangiocardiography is a sensitive and reliable means of proving the absence of significant tricuspid regurgitation, and we did not find TI during the operation in patients in whom RVA showed none. We could not make a positive diagnosis of TI based on angiocardiographic evidence, however, for there were false positives, perhaps in as high as 30 per cent of our cases.

As described, we evaluated the significance of the RA pressure in 27 of our patients proved negative for TI by angiography and in seven proved positive during operation. It was found that atrial fibrillation without TI produced RA pressure contours that have been considered diagnostic of TI. This has probably contributed to the belief that atrial fibrillation is more frequently associated with TI than we found to be the case or than was found by Gould and associates.[11] TI was not associated with atrial fibrillation in the absence of valve deformity or marked RV failure in our patients. We also noted, in agreement with Rubeiz and associates[8] but contrary to the belief of Sherman and co-workers,[13] that with sinus rhythm the X descent can be deeper than the Y even in the presence of TI. With sinus rhythm a right atrial pressure pattern with X deeper than Y does not exclude TI.

We did observe, however, a right atrial pressure contour characteristic of TI as have others before. It has almost no X descent, the C wave leading directly into a large systolic wave. When this is seen, TI is quite likely present, although right ventricular failure gave occasional false positives in our study. This contour did not occur when sinus rhythm was present. In addition to concluding the RA pressure contour to be less helpful than previously described, we found in one case, as described by Rubeiz and associates,[8] that a normal mean RA pressure level could be associated with TI in the presence of sinus rhythm.

Summary

The dependability of RVA in the evaluation of TI was studied in 141 patients with congenital or rheumatic disease. In patients over age 10, angiocardiography revealed TI in 13 and was negative in 27. Eight with positive RVA had cardiac operation and TI was confirmed in seven; three not having been operated upon were probably false positives. Six with negative RVA had an operation and no TI was detected. In 20 per cent of 95 younger patients RVA revealed TI, often believed catheter induced.

RA pressure criteria commonly employed in the hemodynamic diagnosis of TI were tested. RA pressure level and contour were analyzed in 27 cases proved negative for TI by RVA and in seven proved positive by operation. An X descent shallower than Y correlated better with atrial fibrillation than with TI. X deeper than Y correlated better with sinus rhythm than with tricuspid competence.

RVA can exclude TI but yields false positive studies. RA pressure contour is believed not to have the usually accepted significance.

The operations were performed by Dr. Albert Starr, Professor of Surgery and Chief of the Division of Cardiopulmonary Surgery, and members of the Division. The secretarial assistance of Mrs. Ruth Auch is also gratefully acknowledged.

REFERENCES

1. Acevez, S., and Carral, R.: The diagnosis of tricuspid valve disease, AM. HEART J. 34:114, 1947.
2. Cobbs, C. W., Jr.: *In* Hurst, J. W., and Logue, R. B., editor: The heart, New York, 1966, McGraw-Hill Book Co., Inc., pp. 591-593.
3. Cooke, W. T., and White, P. D.: Tricuspid stenosis, Brit. Heart J. 3:147, 1941.
4. Kitchen, A., and Turner, R.: Diagnosis and treatment of tricuspid stenosis, Brit. Heart J. 26:354, 1964.
5. Goodale, F., and Shaw, R.: Functional examination of the heart at utopsy, New England J. Med. 223:719, 1955.
6. Lewis, T.: The mechanism and graphic registration of the heart beat, London, 1925, Shaw and Sons, Ltd.
7. McCord, M. C., and Blount, S. G., Jr.: The

hemodynamic pattern in tricuspid valve disease. Am. Heart J. 44:671, 1952.
8. Messer, A. L., Hurst, J. W., Rappaport, M. B., and Sprague, H. B.: A study of the venous pulse in tricuspid heart disease, Circulation 1:388, 1950.
9. Müller, O., and Shillingford, J.: Tricuspid incompetence, Brit. Heart J. 16:195, 1954.
10. Bristow, J. D., Kloster, F. E., Herr, R., Starr, A., McCord, C. W., and Griswold, H. E.: Cardiac catheterization studies after combined tricuspid, mitral and aortic valve replacement, Circulation 31:437, 1966.
11. Braunwald, N. S., Ross, J. J., and Morrow, A. G.: Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement, Circulation (Suppl. III) 34:63, 1966 (abstr.).
12. Parker, B. M., Hudson, H. L., Smith, R. M., and Friedenberg, M. J.: Tricuspid and mitral insufficiency in normal dogs, Circulation (Suppl. II) 32:168, 1965 (abstr.).
13. Sherman, W. T., Ferrer, M. I., and Harvey, R. M.: Competence of the tricuspid valve in pulmonary heart disease (cor pulmonale), Circulation 31:517, 1965.
14. Hurst, J. W., and Schlant, R. C. In Hurst, J. W., and Logue, R. B., editors: The heart, New York, 1966, McGraw-Hill Book Co., Inc., p. 88.
15. Ferrer, M. I., and Harvey, R. M.: Hemodynamic aspects of cardiac arrhythmias in man, Am. Heart J. 68:153, 1964.
16. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Cournand, A., and Richards, D. W., Jr.: Hemodynamic studies in rheumatic heart disease, Circulation 6:688, 1952.
17. Sepulveda, G., and Lukas, D. S.: The diagnosis of tricuspid insufficiency, Circulation 11:552, 1955.
18. Rubeiz, G. A., Nassar, M. E., and Dagher, I. K.: Study of the right atrial pressure pulse in functional tricuspid regurgitation and normal sinus rhythm, Circulation 30:190, 1964.
19. Lanning, A. M., Mailh, N., and Leight, L.: Mitral regurgitation and intramyocardial injection resulting from left heart catheterization, Am. Heart J. 71:495, 1966.
20. Sobol, B. J., Bottex, G., Emirgil, C., and Gissen, H.: Valvular insufficiency occurring during cardiac catheterization, Am. J. Cardiol. 14:533, 1964.
21. Braunwald, E., Brockenbrough, E. C., Talbert, J. L., Folse, J. R., and Rockoff, S. D.: Selective left heart angiocardiography by the transseptal route, Am. J. Med. 33:213, 1962.
22. Gould, L., Weber, D., Schaffer, A. I., and O'Connor, R. A.: Does atrial fibrillation lead to tricuspid insufficiency? Am. J. Cardiol. 16:189, 1965.

Non surgical complete heart block associated with aortic stenosis: The importance of correct diagnosis

Jonathan O Parlain M D
*John Brantley Sydnor B.A ***
Charlottesville Va

The association of aortic stenosis of various etiologies and nonsurgical acquired complete heart block is a relatively well recognized although poorly understood combination of clinical phenomena. The pathogenesis of the associated complete heart block has been variously ascribed to (1) extension of calcium from the calcified aortic valve into the Purkinje system as initially described by Yater and Cornell in 1935[1] Boas, and later by Warshawsky and Abramson and more recently by Cobbs[4] (2) prolonged mechanical stress with injury and eventually secondary fibrosis of the conductive tissue as proposed by Friedberg and co-workers and Lev[4] and (3) also anoxia of the bundle caused by functional coronary insufficiency.[12] However no clear cut impression of the exact mechanism involved is apparent probably indicating that a combination of the above-outlined possibilities is important in all cases of aortic stenosis and nonsurgical complete heart block. Recent clinical reviews have shown the incidence of congenital or rheumatic valvular disease in complete heart block to range from 3 per cent[1] 8 per cent[14] to 10 per cent although the reverse correlation does not appear as high

The present article concerns three cases of aortic stenosis and nonsurgical acquired complete heart block seen at the University of Virginia Hospital with special emphasis on diagnosis and management in various clinical situations.

Clinical material

The medical records of all patients with diagnosed aortic stenosis admitted to the University of Virginia Hospital from January 1961 through August 1966 were reviewed. Of 384 patients records studied three patients were found with a combination of proved aortic stenosis and electrocardiographically documented nonsurgical acquired complete heart block. All patients in this study were seen by the authors, and their clinical profiles are presented

Case 1 F H L. (UVAH No. 56-31-40), a 33-year-old office messenger was admitted to the University of Virginia Hospital for the first time in July 1966 after having experienced three syncopal episodes all unrelated to activity during the preceding three months. Although he recalled vague growing pains at the age of 4 years he was unaware of rheumatic fever chorea, prolonged fever or unusual childhood illnesses. There was no knowledge of cardiac disease until three months prior to admission, when he was informed of a heart murmur

From the Department of Medicine University of Virginia School of Medicine Charlottesville Va
Received for publication April 26, 1967
Instructor Department of Internal Medicine, University of Virginia School of Medicine.
**Fourth-year medical student, University of Virginia School of Medicine.

and moderat hypertension on routine medic l evaluation. He was completel free of symptom prior to the syncope.

At the time of admission his pulse as 56 per minute and irregular and his blood pressure was 160/110. The carotid pulses ere slow-rising but f ll, and there was forceful apical impulse 2 cm. to the left of the midclavicular line. The second heart sound over the aortic area as definitely diminished in intensity and there as grade 4/6 harsh, ejection-quality syst lic murmur loudest t the aortic area, but heard over the entire precordium and into the neck. Diastole was clear. The neck eins ere flat. An electrocardiogram showed sinus rhythm ith intermittent complete heart block with slow idioventricular focus. The chest x-ray (Fig. 1) showed probable left entricular hypertrophy and cardiac fluoroscopy revealed extensive calcification of the flattened aortic alv leaflets extruding int the area of the aortic ring.

On the morning of admission after another episode of complete heart block and associated Adams-Stokes syncope, transvenous catheter pacemaker was inserted. Because of the dense aortic valvular calcification, diminished aortic second sound, probable left entricular hypertrophy on physical examination and slow-rising carotid pulses, together with the characteristic murmur severe aortic stenosis as thought to be so likely that cardiac catheterization was felt unwarranted. On the sixth hospital day the insertion of Starr-Edwards aortic h prosthesis and Cordis trial-synchron pacemaker was carried out thout incident. At the time of surgery the aortic h as noted to be totally immobile and completely calcified th small fish-mouth opening. Postoperati ely the patient recovery as complicated by right lower lobe pulmonary embolus and the development of false aneurysm of the left femoral art ry t the sit of arteriotomy both conditions responded to usual measures without chronic debility. H has subsequently been followed under close medical supervision on long-term anticoagulation ithout cardiac symptoms, and no evidence of aortic incompetence or further syncope. Many lectrocardiograms ha e show normally f nctioning trial-actu ted pacemaker. Total follow-up period now is 11 months.

Comment. The separation of linical symptoms secondary to aortic stenosis from those of complete heart block is a perplexing but most important problem of differential diagnosis in this era of increasingly effecti cardiothoracic surgery. The common denominator of syncope hich these tw entities often demonstrate is reported to occur lassically on exertion or change in position in aortic stenosis, but more likely to ppear without apparent tecedent cause hen due to typical Adams-Stokes attacks with complete heart block or other arrhythmias. Such differentiation is not completely effective, however and the problem becomes especially difficult i the case of strongly suspected aortic tenosis and intermittent, complet heart block such as the bov patient demonstrated. I this patient, the many parameters suggesting severe aortic stenosis (nearl normal blood pressure dense aortic alv calcification with flattened relativel immobile aortic leaflets, diminished aortic second sound, delayed carotid pulse palpable left entricular hypertrophy on ph sical examination, and probable left entricular hypertrophy on chest -ray) precluded the necessity of confirmation by cardiac catheterization. Such dilemma arrants surgical correction of both possibilities (i.e. simultaneous correction of the stenotic aortic valve and insertion of permanent pacemaker), inasmuch as differentiation of either problem from the other is incomplete. Mahaim has demonstrated, however at least partial improvement of second degree heart block following aortic alvuloplasty and Cobbs tates that intermittent complete heart block has been relieved by removing an offending calcium spicule t the time of aortic valvotomy. No other description of sim lar surgical success could be found.

Case 2. C. E. M. (UVAH No. 56-46-65), 48-year-old industrial plant supervisor as admitted to UVAH for the first ime in August, 1966 after several syncopal episodes hich were unrelated to exertion and occurred over the preceding three months. He gav history of heart murmur hich as first detected t the age of 16 years, but had no knowledge of rheumatic fever chorea, childhood arthritis, or unusual infantile illnesses. He had been free of symptoms til the onset of syncope.

At the time of admission, he had complete heart block ith regular rate of 40 and blood pressure of 130/70. The apex beat as 2 cm. to the left of the midclavicular line and there was prominent systolic thrill over the aortic area. The carotid pulses ere full. The second heart sound over the aortic area as of normal intensity. There was grade 4/6 harsh, ejection-type systolic murmur ith an associated ejection click, loudest at the aortic area, radiating over the entire precordium. A grade 1/6 diastolic murmur was heard only in the sitting



Fig. 1. Patient 1. AP hest -ray hich show probable ev lenc of left entricular enlargement even on AP film.



Fig. 2. Patient 2. PA chest x-ray shortly after admission showing moderate left ventricular enlargement and slight dilatation of ascending aorta.



Fig. 3. Patient 3. PA chest x-ray obtained in December 1960 showing obvious left ventricular enlargement.

position at the lower left sternal border. There were no signs of increased venous pressure. An electrocardiogram showed complete heart block with a slow idioventricular rate of 48 and a left bundle branch block configuration. Chest x-ray (Fig. 2) showed moderate left ventricular hypertrophy, dilatation of the ascending aorta, and a slightly calcified aortic valve. Fluoroscopy confirmed the chest x-ray findings, and although the aortic leaflets were surrounded by minimal calcification they were noted to be very mobile.

An isoproterenol infusion maintained the ventricular rate between 44 and 52 until a transvenous catheter pacemaker was inserted. Right and left cardiac catheterization was subsequently carried out revealing a peak-systolic aortic gradient of 38 mm. Hg (LV 138/7, AO 100/70) and a cardiac index which was slightly reduced (2.54 L. per minute per square meter[4]). Because of the mild aortic systolic gradient and only slightly diminished cardiac index, it was felt that the complete heart block, and not aortic stenosis, was responsible for the syncopal episodes. Two days after cardiac catheterization, a permanent Chardack-Greatbatch pacemaker was inserted by means of a left thoracotomy. The patient's recovery was uneventful, and he was discharged the fifteenth hospital day totally asymptomatic. With total follow-up of seven months, he has continued syncope-free with a normally functioning fixed rate pacemaker at 72 per minute.

Comments. This patient, in whom complete heart block was not accompanied by such obvious findings of aortic stenosis (i.e., only a slightly calcified aortic valve with very mobile valve leaflets, no diminution of the aortic component of the second heart sound, no delay in carotid pulse), cardiac catheterization provided the information necessary to assign primary responsibility for syncope to the complete heart block (peak aortic gradient was only 38 mm. Hg and cardiac index only slightly reduced at 2.54 L. per minute per square meter[4]), thus enabling eventual surgical correction to be directed only at the arrhythmia.

Case 3. R. E. H. (UVAH No. 48-01-46), a 72-year-old farmer, was first seen at this hospital in December 1960 having been referred here because of several episodes of lightheadedness and syncope. These episodes occurred with increasing frequency during the 24 hours prior to his first admission, and were not related to exertion, and were not accompanied by chest pain or dyspnea. He had been completely well prior to the onset of the syncopal episodes, and there was no past history of known rheumatic fever or known cardiac disease.

At the time of his initial admission his pulse was regular at 50 per minute, and the blood pressure was 200/110. The heart border and PMI could not be determined. The carotid pulses were full and the second sound over the aortic area were of normal intensity. There was a grade 3/6 ejection type systolic murmur at the apex which was also heard along the left sternal border and the aortic area radiating prominently into the neck. Diastole was clear and there were no signs of increased venous pressure. An electrocardiogram showed intermittent episodes of complete heart block varying with lesser degrees of A-V block. The chest x-ray (Fig. 3) showed left ventricular hypertrophy.

On supportive treatment he remained asymptomatic with ventricular rates of 40 per minute. The etiology of the heart block was uncertain, but aortic

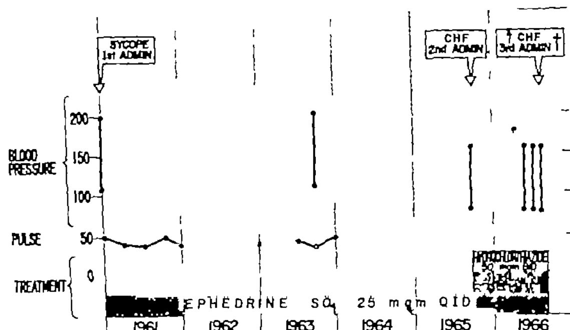


Fig. 4. Clinical course of Patient 3 demonstrating slowly decreasing blood pressure, unchanged heart rate.

tenosis was considered as possibly contributing to the syncopal episodes because of the heart murmur. However, without further corroborative evidence for this, investigation in this area was not attempted. The patient was subsequently discharged, and followed in the medical outpatient department at regular intervals on Ephedrine sulfate 25 mg. four times a day (Fig. 4), with no further episodes of syncope and excellent exercise tolerance until September, 1965, when he developed dyspnea, pedal edema, and abdominal distention. He was admitted for a second time. The blood pressure was 200/90 and pulse 54 and regular. The carotid pulses were thought to be normal in quality and there were moist râles at both lung bases posteriorly. The heart was enlarged without definite left ventricular prominence. A harsh grade 2/6 systolic murmur was heard at the base with radiation into the neck. The aortic component of the second heart sound was diminished. There was ascites and massive peripheral edema. An ECG was unchanged from before showing complete heart block with an idioventricular focus at 52 per minute. The etiology of his congestive heart failure was not established, but he responded dramatically to digitalization and diuresis with 19 kg. weight loss over a nine day hospitalization.

Within six months, however, increasing peripheral edema and dyspnea necessitated more vigorous attempts at diuresis which were only transiently effective. His final admission in August, 1966 was necessitated by increasing shortness of breath and possible digitalis intoxication. At that time the blood pressure was 140/70, pulse was 50 and regular and there was moderate jugular venous distention. The chest revealed fine basilar râles and the heart was unchanged from before except that even more cardiomegaly was noted. An ECG was unchanged with low idioventricular pacemaker at 50 per minute. Attempts at diuresis and optimal digitalization were begun, but the patient suddenly developed ventricular tachycardia which quickly degenerated into ventricular fibrillation on the fourth hospital day. Attempts at resuscitation were unsuccessful. An autopsy was performed five hours after death.

The heart was tremendously enlarged secondary to left ventricular dilatation and hypertrophy, weighing 950 grams. The aortic valve cusps were partially fused and calcified (Fig. 5), with a cross-sectional area of less than 1 sq. cm. The coronary arteries were only slightly sclerotic but there was focal myocardial scarring scattered through the anterior wall of the left ventricle and the interventricular septum. The aorta was severely atherosclerotic and the lungs were congested and edematous (total weight 1,400 grams).

Microscopic examination of the myocardium including special sections in the region of the A-V node, penetrating portion of the bundle of His, beginning of the branch bundle and portions of the right and left bundle branch, revealed diffuse marked fibrosis involving areas of the A-V node and bundle of His, although these structures themselves could not be definitely identified. No calcification was detected in this area.

Comment. In this patient, complete heart block was documented many years before there was clinical evidence of significant aortic stenosis, a well-recognized sequence of developments emphasized by Cobbs. With advancing severity of aortic valve obstruction, as recognized by decreasing



Fig. 5. Aortic valve of Patient 3 as viewed from above which reveals thickening of the cusps and several prominent deposits of calcium.

blood pressure, diminishing aortic second sound, and enlarging cardiac silhouette. Intractable congestive heart failure followed, with death in part also probably due to digitalis toxicity. Harris and associates[14] emphasized that the murmur of increased stroke volume in complete heart block may resemble that of aortic stenosis and that relative hypotension, as demonstrated by this patient, should be an important clue to the diagnosis of underlying aortic stenosis. Earlier attention to this axiom in this patient could have resulted in surgical correction of the hemodynamically significant aortic stenosis. An additional point to be emphasized is that transvenous pacing during the patient's last admission might have been effective in reversing the severe congestive heart failure prior to definitive treatment.

Pathogenesis

Although complete heart block occurs in calcific aortic stenosis, the pathogenesis is not as simple as superficial inspection would suggest. Lenègre[1] has shown that prolonged mechanical stress with eventual injury and secondary fibrosis of the conduction system, rather than coronary artery disease as previously suspected, may be the most important causative factor in nonsurgical acquired complete heart block. In his 37 cases subjected to histopathological study including serial sectioning of the conduction system, only 10 cases of occlusive or stenotic coronary atherosclerosis were found and only 6 cases with significant disease of the artery to the A-V node. Moreover, when septal infarction or fibrosis resulted from coronary artery disease, the lesions were generally distant from the conduction system, whereas lesions responsible for the heart block were confined discretely to the conduction tissue while the adjacent septal muscle was intact. He reasoned that this negative correlation between coronary atherosclerosis and conduction system lesions suggested an alternate relationship—that the conduction system lesions may be due to fibrosis secondary to prolonged mechanical stress rather than ischemia. Gilchrist's[12] experience with sudden abrupt development of complete heart block in two patients with aortic valvular involvement provides some support for this theory by implying that the block is due to mechanical stretching and distortion of the conduction system rather than gradual extension of calcium from the region of the aortic valve. Certainly long-standing aortic stenosis provides the necessary background of mechanical stress thought so important by these authors in the pathogenesis of complete heart block.

In the third patient of this series whose myocardium was studied in detail, no evidence of septal calcification was detected despite a heavily calcified aortic valve. Instead, diffuse and heavy scarring throughout the area of the A-V node and bundle of His was detected, supporting Lenègre's hypothesis of prolonged mechanical stress producing eventual injury and secondary fibrosis of the conduction system.

Diagnosis

In the presence of complete heart block the clinical assessment of aortic stenosis becomes more difficult than usual. The history of syncope following exertion or change in position[9] should provide very helpful information toward establishing the diagnosis of aortic stenosis, but was not found in any of the three patients in this series. Likewise, no other historical findings proved helpful in this differential diagnosis. On physical examination, the systolic ejection murmur due to a large stroke volume commonly heard in complete heart block precludes the detection of a similar systolic murmur characteristic of aortic valve obstruction. The blood pres-

sure was, however in all cases in the present series lower than would have been anticipated in complete heart block with a slow ventricular rate a diagnostic point emphasized by Harris and associates. This finding is therefore highly suspicious of aortic valve obstruction and should be of great help to the clinician in alerting him to the presence of aortic stenosis in addition to complete heart block. Left ventricular hypertrophy (definitely present in only Patient 1 of the present series) a small amplitude and slowly rising carotid pulse (also present in only Patient 1 of the present series) or a diminished aortic component of the second heart sound (present in Patients 1 and 3 of the present series) were of only ancillary help in authenticating the presence of aortic stenosis in our patients. Other helpful information was provided by chest x ray revealing definite left ventricular hypertrophy in Patients 2 and 3 and probable evidence of left ventricular hypertrophy in Patient 1 Image intensification cardiac fluoroscopy was diagnostic in both patients so studied (Patients 1 and 2) and was instrumental in arriving at the correct diagnosis that both complete heart block and aortic stenosis were present

Therefore the finding of relatively low or normal blood pressure in a patient with complete heart block whose blood pressure and pulse pressure would be expected to be elevated by the high stroke volume in complete heart block alone—should alert the clinician to the possibility of underlying aortic valve obstruction This finding together with left ventricular hypertrophy on chest x ray and the demonstration of aortic valve calcification by cardiac fluoroscopy may in some instances be adequate to establish the diagnosis of significant aortic stenosis in the face of complete heart block Nevertheless, cardiac catheterization for confirmation is necessary in most cases such as Patient 2 in the present series.

Management

Once the diagnosis of aortic stenosis is seriously suspected in a patient with complete heart block who has developed a syncopal episode the decision to direct therapy at the arrhythmia alone or at both the arrhythmia and the aortic valve obstruction seems to be best dictated by evaluation of the severity of the aortic stenosis. This problem was easily resolved in Patient 1 whose degree of aortic obstruction was clearly hemodynamically significant without having to resort to cardiac catheterization. Patient 2 however did require cardiac catheterization to quantitate the degree of aortic stenosis and indeed the moderate aortic systolic gradient (38 mm Hg) and slightly reduced cardiac index of 2.54 L. per minute per square meter[3] was felt to be not significant enough to warrant aortic valve surgery at that time Therefore the patient received only a permanent transthoracic pacemaker implantation Unfortunately the diagnosis of aortic stenosis was not seriously enough considered in Patient 3 until his final brief admission

The consideration that complete heart block in association with aortic stenosis, especially in younger individuals, might actually be caused by septal ischemia[11] rather than septal fibrosis could be used as an argument to attempt correction of complete heart block in such patients by repair of aortic valve obstruction alone. This was the concept which Mahaim thought important when he described a case of partial AV block in association with aortic stenosis which improved to only first degree AV block following aortic valvuloplasty however the total follow up of this case was only six months making interpretation of a condition as unpredictable as AV block somewhat difficult Cobbs, in support of this same idea, stated that removal of an offending spicule at aortic valvotomy had relieved complete heart block but did not describe any particular case in detail. Inasmuch as the precise etiology of aortic stenosis in association with complete heart block can never be established in the individual case on clinical grounds alone it is the authors feeling that management of these patients should always include treatment of the rhythm disorder Proper therapy should therefore be individualized in each case with some patients requiring aortic valve surgery in addition to a permanent pacemaker and others requiring only a pacemaker Despite Mahaim's and Cobbs's

apparent success in relief of heart block by attack on the aortic valve alone such a circumstance would have to be very unusual and cannot be recommended as the sole procedure in patients with both aortic stenosis and complete heart block.

Summary

Three cases of definitely established aortic stenosis associated with nonsurgical acquired complete heart block seen at the University of Virginia Hospital are presented. Emphasis is placed on the difficulty in diagnosing aortic stenosis in the presence of complete heart block, and upon the importance of establishing this diagnosis in deciding upon the most appropriate therapeutic approach in each clinical situation.

The single patient who died was found to have diffuse myocardial fibrosis in the region of the A-V node and bundle of His rather than extension of calcium from the heavily calcified aortic valve as the probable explanation for complete heart block.

The authors would like to express their sincere appreciation to Dr. William M. [illegible], of the Department of Pathology of the University of Virginia School of Medicine, for his great help with the pathological material relevant to the third patient in this series, and to Dr. J. [illegible] R. Beckwith for review of the manuscript.

REFERENCES

1. Y ter W M and Cornell, V H Heart block due to calcareous lesions of the bundle of His review and report of case with detailed histopathological study Ann. I t Med. 8 777 1935
2. Boas, E P Angina pectoris and heart block as symptoms of calcareous aortic stenosis, Am J M Sc 190:376, 1935
3. Warshawsky H and Abramson, W Complete heart block in calcareous aortic stenosis, A n. I t. Med. 27 1040 1947
4. Cobbs, B : Clinical recognition and medical management of rheumatic fever and valvular heart disease Hurst and Logue, editors: The Heart, New York, 1966 The Blakiston Company p. 569
5. Friedberg C. K. Donoso, E., nd Stein, W G. Non-surgical acq ired heart block, Ann. New York Acad. Sc. 111 art. 3 835 1964.
6. Lev M The normal anatomy of the conduction system in man and its pathology in A V block, Ann. New York Acad Sc. 111:817 1964
7. Gallavardin, L. Lyon méd. 151:217 1933 Arch. d. mal. d coeur 30 745 1937
8. Friedberg, C. K. Diseases of the heart ed. 3, Philadelphia, 1966 W B. Saunders Company p 1138.
9. Mahaim, Ch. De la réduction d'un bloc A V par la correction chirurgicale d no stenose ortique, Cardiologica (Basel) 42 141 1962.
10. Harris, A. M Sleight, P and Drew C. E. The diagnosis and treatment of aortic stenosis complicated by heart block, Brit. Heart J 27:560 1965
11. Lenègre J Les blocs auriculo-ventriculaires complets chroniques. Études des causes et des lesions à propos de 37 cas, Mal. Cardiovas. 3:311 1962.
12. Gilchrist, A. R. Clinical aspects of high-grade heart block, Scott. M J 3:62 1958.
13. Friedberg C K Disturbances in conduction heart block and bundle branch block, I Diseases of the heart ed. 3, Philadelphia, 1966, W B Saunders Compa y p.596.
14. Penton, G. B Miller H and Levine, S. A. Some clinical features of complete heart block, Circulation 13:801 1956.
15. Wright, J C., Hejtmancik, M R., Herrmann, G R. and Shields, A. H. A clinical tudy of complete heart block, Am Heart J 52:369 1956.
16. Curd, G. W J et al.: Etiology of trioventricular heart block study of relevance to prognosis nd pacemaker therapy Cardiovas. Res. Bull. (Baylor U iv) 1:63 1963

Prediction of right ventricular pressure in pulmonic stenosis from sponge vectorcardiogram and electrocardiogram

A. C. Witham, M.D.
R. L. Rainey, M.D.
J. H. Edmonds, Jr., M.D.
Augusta, Ga.

Measurements from the Frank vectorcardiogram (VCG) have been shown to correlate well with right ventricular pressure (RVP) in isolated pulmonic stenosis. The present study is of additional interest for several reasons. The age span of the patients is wider and the analysis is therefore a more demanding test of vectorcardographic methods of assessing hemodynamics. The lead system employed utilizing sponge electrodes, probably shares the advantages of other grid systems over that of Frank but has received little clinical attention.[-4] This report also presents further development of a system of quantitative vectorcardiography based on loop morphology.[5] Computer analysis has permitted scanning of numerous correlations so that many doubts concerning undetected relationships can be resolved. Many conclusions of the earlier study with the Frank VCG have been confirmed using a different lead system, technique of mensuration and patient material. Methods for predicting RVP satisfactorily from simple vector measurements have been indicated and stepwise multiple regression analysis has yielded an equation combining VCG and electrocardiogram (ECG) measurements which allows better prediction than any single variable.

Materials and methods

Patients. A total of 21 patients from 1 to 53 years of age had complete right heart catheterization and VCG's (Table I). None was in heart failure or had ECG patterns of complete right bundle branch block. All but one with RVP greater than 80 mm. Hg had diagnostic confirmation at open heart surgery.

Hemodynamics. The following seven measurements or standard calculations were used: (1) right ventricular systolic pressure (RVP), (2) maximum systolic gradient across pulmonic valve, (3) calculated valve orifice size, (4) planimetrically integrated right ventricular pressure during ejection (MEP), (5) right ventricular flow in liters per minute per square meter, (6) right ventricular stroke

From the Division of Cardiology, Department of Medicine, Medical College of Georgia, and Eugene Talmadge Memorial Hospital, Augusta, Ga., 30902.
Supported in part by United States Public Health Service Research Grant X HE 07266 and FR-00961-03.
Received for publication Feb. 28, 1967.

Table I. Selected hemodynamic, VCG, and ECG measurements

Patient, (age and sex)	RVP (mm. Hg)	TTI	SW (kg.-m./M²)	MEP (mm. Hg)	Dur S-LP (msec.)	S-LP/QRS (msec./msec.)	Sum S_f (mv.)	Max. S/R_f (mv./mv.)	$M\angle_f$ (degrees)	Max. S (mv.)
S. C. 27F	35	631	1.14	26	25	0.32	0.47	0.25	23	0.46
S. C. 5F	40	851	2.62	33	18	0.27	0.83	1.00	123	0.82
G. N. 14M	44	657	2.11	33	22	0.35	1.19	0.29	59	0.20
K. U. 14M	48	596	1.71	32	13	0.19	0.50	0.23	50	0.32
G. S. 17M	50	890	2.22	50	44	0.44	1.60	0.69	38	0.80
C. R. 3M	53	945	3.69	42	20	0.29	0.90	0.86	33	0.26
C. R. 28M	55	894	1.41	34	30	0.34	1.67	0.80	89	1.07
R. B. 17M	58	962	3.55	44	24	0.26	1.23	1.03	244	0.94
S. O. 14F	60	1,415	2.58	42	24	0.32	0.94	1.21	161	0.93
T. J. 2F	66	1,203	2.84	46	20	0.28	0.72	0.32	74	0.85
E. C. 5F	70	1,567	4.65	47	26	0.41	1.80	0.45	63	1.00
L. O. 1M	73	1,694	3.50	61	24	0.35	1.50	0.95	22	1.50
H. O. 22F	75	1,361	3.41	66	30	0.39	1.23	0.44	57	0.83
B. B. 15M	80	1,297	5.01	55	35	0.34	0.90	0.28	56	0.30
D. F. 26M	113	2,102	3.62	78	32	0.36	1.72	3.49	175	1.65
J. C. 60M	118	2,059	3.47	85	45	0.43	1.62	1.92	182	1.05
S. T. 11F	122	2,377	5.82	85	44	0.43	2.86	2.18	173	2.03
J. S. 23M	130	3,050	6.12	125	38	0.47	2.47	1.90	120	2.33
G. S. 53M	132	3,512	5.52	129	34	0.47	3.20	2.02	144	2.45
P. A. 83M	160	2,822	8.03	114	35	0.48	3.08	1.67	160	3.31
R. B. 34F	172	2,506	4.33	119	46	0.63	2.93		195	2.03

work in kilogram meters per square meter (SW) (7); time tension index = MEP × duration systole × heart rate (TTI).[7]

Vectorcardiogram. Frontal (fp), horizontal (hp), and right sagittal (sp) loops were recorded as previously described[8] during hospital admission for cardiac catheterization. Examples are shown in Fig. 1. In a given patient, loops in all planes were recorded with the same gain. The angular position of each vector was recorded in a clockwise manner from 0 to 360 degrees starting at the right tip of the horizontal coordinate in each planar diagram.

A major change in direction was defined as at least 75 degrees in two or more planes. The following QRS vectors were identified: Q (initial change in direction), R (maximum leftward extent of loop), S (first major change at least 12 msec. after R), S′ or S″ (further major changes in direction after S at least 12 msec. apart), 20 msec. (20 msec. after beginning of loop), M (maximum vector in each plane).

For each vector, its time of appearance, planar and spatial voltages, and angular positions were recorded. M was identified in each plane, its voltage and direction noted ($M_{f,h}$ and $M\angle_{f,h}$, etc.), and the spatial voltage of the largest was calculated (M_3).

In addition, the following were recorded: the total duration of QRS (QRS), duration of the S loop, i.e., from the S point to the beginning of the T loop (Dur S-LP), the ratio of S loop duration to total QRS (S-LP/QRS), the angles and voltages of the largest S in fp and hp (Max. $S_{f,h}$), sum of S vectors in fp (Sum S_f), maximum S/R voltage ratio in fp and hp (Max. $S/R_{f,h}$), largest spatial S vector (Max. S_3), sum of spatial S vectors (Sum S_3), ratio of maximum spatial S to spatial R voltage (Max. S_3/R_3), duration of anterior forces, ratio of time anterior to total QRS, and an angle between S and R vectors in the horizontal plane (S-R$\angle_h$).

The original data sheets contained 70 spaces for VCG measurement and the derived and overlapping values described above. S′ vectors were noted in 14 instances, and S″ on only three occasions. No R vector was found in one patient with severe stenosis.

S-R∠-A (degree)	S∠-A (degree)	Max. S (mv.)	S' (mm.)	Sum S (mm.)	Max. S/R (mm./mm.)	S_I (mv. × 10)	R_{aVR} (mm. × 10)	$S + R_{V1}$ (× 10)	R/S_{V1} (mv./mv.)
263	346	0 46	0 30	0 96	0 40	2	2	4	0 4
181	223	1 10	0	1 30	0 97	5	10	15	1 4
236	270	0 74	0 54	1 28	0 23	2	3	4	0 2
220	215	0 62	0	0 82	0 24	1	8	7	0 5
145	173	0 96	0 79	1 65	0 66	6	6	12	5 8
248	246	0 95	0	0 95	0 89	1	5	6	1 6
180	211	1 07	0 77	1 84	0 76	6	10	16	10 6
205	226	1 44	0	1 44	1 18	6	9	15	8 5
173	157	0 93	0	0 95	1 20	7	6	13	1 2
175	218	0 85	0	0 85	0 37	6	17	23	1 7
142	165	1 05	0 92	1 97	0 43	10	17	27	2 2
115	175	1 77	0	1 77	0 81	10	25	35	25 0
172	210	0 88	0 42	1 30	0 44	6	5	11	2 2
184	197	0 50	0 43	0 93	0 26	3	9	12	0 8
160	229	1 67	1 02	2 69	2 39	7	8	15	0 8
120	198	1 06	0 58	1 91	1 62	5	11	18	10 5
99	144	2 04	1 27	3 31	2 04	15	35	53	35 0
47	116	3 04	0 49	3 53	1 67	16	37	83	37 0
60	141	2 78	1 01	3 79	1 33	10	29	39	29 0
65	120	3 31	1 51	4 82	1 82	18	45	66	6 0
	123	2 15	2 15	3 45		11	12	23	1 1

Electrocardiograms. An ECG was recorded on the same hospital admission. The following ten indices of right ventricular overload were measured: Mean QRS axis, depth of S in Lead I, height of R in Leads aVR and V, sum of R_V and S_I, ratio of R to S in Lead V, ratio of R to S in Lead I, difference between R and S voltage in Lead V, largest P wave amplitude in Leads II or III, and product of P positivity in Lead V times its duration.

Analysis of data. A preliminary probe for correlation was obtained on the first 16 patients and certain variables were eliminated from further consideration either because correlations were poor or added little.

Four hemodynamic parameters, 31 vector and 5 ECG measurements were selected as most promising and coefficients of correlation (r) were obtained between them by a standard program on all 21 patients. A total of 26 of the more interesting linear correlations were plotted and scrutinized for the possibility of improving r by semi-log or log log plots, but this did not appear helpful. A stepwise multiple regression analysis was also performed with one dependent variable (RVP) and eight independent variables selected because of their relatively independent derivation and significantly high r with RVP. They included six VCG and two ECG measurements: S-LP/QRS Max.∠, S_I, R, S∠-A, S-R∠-A, Sum S_H, R_{V1}, and S_I.

Results

Table I contains individual measurements of special interest. Although numerous significant correlations were found, the parameters presented are those which gave the highest r values between hemodynamic and VCG or ECG variables. A few others will be mentioned in the text. Table II is a matrix indicating r between the 4 hemodynamic, 12 VCG, and 4 ECG variables of Table I.

Correlations with RVP, MEP, and TTI. The highest correlations with RVP are with the voltage of the S vectors (r = 0 87 – 0 90). Although the best is with their spatial sum, it is almost as good with their sum in the fp (Fig. 2). The angle of S_A tends to swing anteriorly with increasing pressure (r = −0 83). In

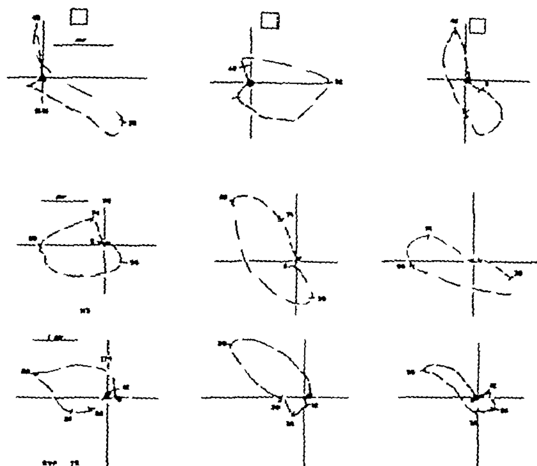


Fig 1 Example of vectorcardiograms from patients with mild, moderate and severe stenosis Frontal (*F*), horizontal (*H*) and sagittal (*S*) planes are displayed from left to right The interruptions are at 4 msec intervals and the points of the dashes denote direction of transcription. P and T loops have been deleted. The *numerals in parentheses in the loops* denote duration of the QRS complex The other numerals represent the timing consecutively of Q R S, S′ or S″ vectors, except in Fig C where there is no R vector Right ventricular pressure and 1 mv calibration is noted near each loop. Each case may be identified in Table I for details (*A*) The loops of this patient with mild stenosis are nearly normal. Counterclockwise rotation in frontal and horizontal planes is preserved. S, however is abnormally large and suggests mild right ventricular hypertrophy (*B*) In this patient with moderate stenosis there are striking abnormalities indicating increased influence of the right ventricle. The R vector is small, appears early, is abnormally anterior and rotation is clockwise in *fp* and *hp* The S vector is large to the right, but still posterior and the S loops in *fp* and *hp* rotate clockwise The maximum spatial vector is S An S′ vector is identified at 74 msec. by its sharp change in direction in *fp* and *sp* (*C*) In this patient with severe stenosis little evidence of left ventricular activation is apparent The Q vector is abnormally leftward, and there is no further evidence of leftward forces. The initial change in direction after Q is distinctly to the right and has therefore been labelled S There are two further sharp changes in direction at 36 and 50 msec which have been labeled S′ and S″ Note that the maximum vector is at 50 msec. and is posterior Loops in both *fp* and *hp* are clockwise Both the magnitude of the maximum S vector and the sum of S vectors indicate a very high pressure

severe overloads R also is more anterior than usual (Fig 1) but its position does not correlate linearly with pressure over the entire range Nevertheless, when these two observations are combined by measuring the "wide" angle between S and R in the hp a better correlation is found than with the S angle alone (Fig 3)

In severe overloads, several other abnormalities appear which have little or no linear correlation with pressure over the entire range. One is the tendency for the Q vector to be directed towards the left Others are for the R vector to appear sooner to be smaller or even to disappear (Fig 1) The total QRS duration is not

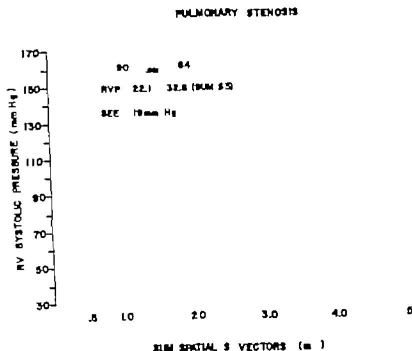


Fig. 2A The sum of the spatial S vectors has the highest correlation of any single variable with right ventricular systolic pressure.

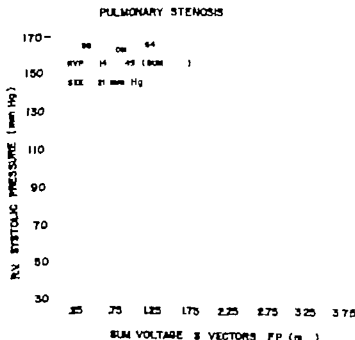


Fig. 2B The correlation is almost as good with the sum of the same vectors in the frontal plane projection.

Table II Coefficients of correlation (r × 100) between important hemodynamic VCG and ECG

	Dur S-LP	S-LP/QRS	Sum S_y	Max S/R_f	M∠ f	Max S	S-R∠
RVP	67	80	88	73	57	87	89
TTI	48	70	84	71	51	88	84
SW	44	58	76	48	41	78	68
MEP	62	80	88	70	52	87	89
Dur S-LP		81	65	44	0	45	61
S-LP/QRS			84	47	0	68	0
Sum S				65	50	90	88
Max S/R					70	69	61
M∠						53	48
Max. S							85
S-R∠							
S∠							
Max S_1							
S'							
Sum S							
Max. S_1/R							
S_1							
R							
S_1 + R							

05 01 0 001 0 33 0 64 Coefficients with p 0 05 recorded as 0.
*n 20 05 0 001 0 2 34 0 65 Underlined nos. indicate negative correlations.

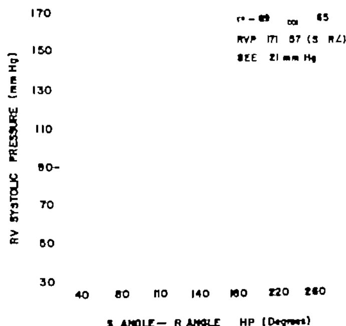


Fig. 3. The wide angle between S and R vectors progressively closes with increasing right ventricular pressure as both swing anteriorly.

variables

S/	Max S	S'	Sum S	Max. S_1/R_1	S_1	R	$S_1 + R_1$	R/S
83	85	76	90	74	76	70	73	49
81	89	56	87	70	80	78	80	67
74	81	52	81	55	88	84	85	49
84	89	68	90	69	76	72	75	58
54	0	77	59	47	43	0	0	0
47	64	86	78	48	66	47	53	0
83	88	82	97	68	84	76	80	60
45	66	56	70	96	55	47	47	48
0	52	42	52	78	45	0	0	0
84	96	65	96	75	92	87	90	58
93	84	62	85	63	83	84	81	73
	79	63	81	51	87	78	82	59
		55	94	71	88	86	88	64
			55	56	58	86	47	64
				74	87	81	85	55
					65	56	56	51
						90	95	63
							71	72
								66

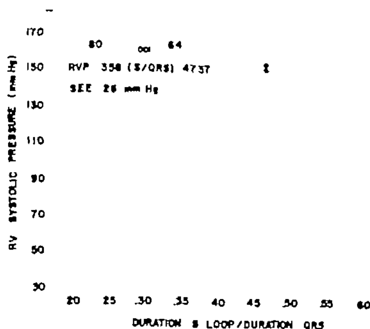


Fig. 3B. Significant correlation exists between the level of right ventricular pressure and the proportion of QRS occupied by the S loop.

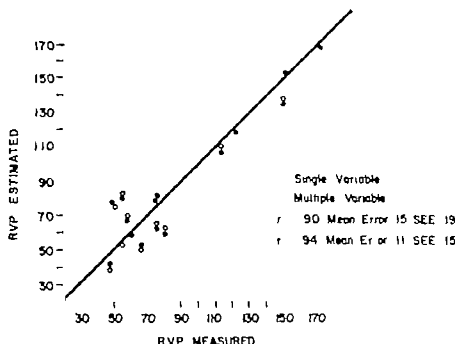


Fig. 4. Comparison of the accuracy of simple and multiple regression equations in predicting right ventricular pressure. The equation using single variable was RVP = 22.067 + 32.782 (Sum S). The equation using multiple variables was RVP = 102.01 + 0.07646 (Max. ∠) + 24.44356 (Sum S_1) − 0.33614 (S-R∠) − 2.93343 (S_1). The only improvement with the latter is in patients with pressures exceeding 100 mm. Hg, but, in this range, is striking. The error of the estimate, however, is significantly smaller over the entire range (t = 1.923; t .05 = 1.725).

prolonged in these patients (mean 83 msec.), but there is a relationship between pressure and both Dur. S-LP (r = 0.67) and S-LP QRS (Fig. 3).

The accuracy of prediction of RVP from several variables (multiple regression) was significantly increased over that afforded by the best single measurement, especially when RVP exceeded 100 mm. Hg (Fig. 4).

For reasons to be considered, the relationships between VCG measurements, MEP and TTI are nearly the same as for RVP.

Correlations with the ECG indices were considerably lower (Table II). The best was with the voltage of S_1 (Fig. 5), which was found to be useful in the multiple regression equation.

Correlations with stroke work. The highest correlations for this parameter were with the same VCG measurements that correlated so well with pressure and its derivatives but were consistently weaker (Table II). Possible reasons will be discussed. Surprisingly, the best correlations of the ECG were with SW (Table II, Fig. 5).

Discussion

Evolution of the VCG in severe pulmonic stenosis. The S vector normally arises from posterobasal septum and the adjacent ventricles.[9,14] Apparently, the right ventricle gradually dominates S as its mass selectively increases. This results in increased voltage and a shift of the S loop towards the anatomical position of the right ventricle, i.e., anteriorly, to the right, and downward. The change in voltage and in position tend to occur simultaneously (r = 0.79) (Fig. 6). With more severe obstructions, S appears earlier, frequently at a time when normally the predominantly left ventricular loop (R) is being inscribed. The S loop becomes more complex with a second or even a third sharp change in direction. These S or S vectors recorded by Frank or sponge leads may be larger than S and be oriented

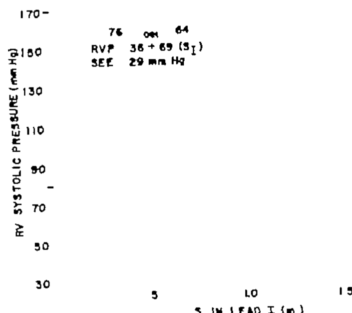


Fig 5A The best correlation bet een ECG indices and right ventricular pressure was with the depth of the S wave in Lead I

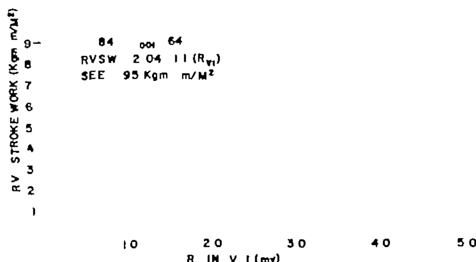


Fig 5B The best correlation bet een ECG indices and hemodynamic parameters was that bet een right ventricular stroke ork and the height of the R in V

posteriorly (Fig 1) n contrast to those recorded by the Grishman cube which accentuates the anterior component of the Z lead The exact origins of S S' and S are not certa n S vectors are not in themselves abnormal for they occur in 15 per cent of normal children and adults. One may infer however that in severe stenosis (Fig 1) the left ventricle is almost silent and the clockwise sweep in the hp and fp reflects activation spreading consecutively from the right septal mass

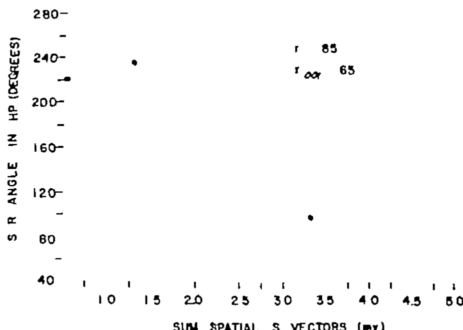


Fig 6A The magnitude of the S ectors increases concomitantly with a change in the angular relationship between S and R in the horizontal plane

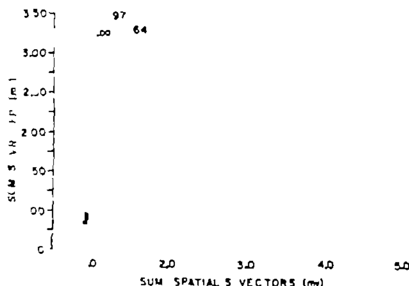


Fig 6B The three dimensional oltage of the S ectors is accuratel reflected in the frontal pl ne

anterior paraseptal area free wall and posterobasal septal region This is the normal sequence for the right ventricle but it ordinarily is obscured by the larger left ventricular forces * The secondary S vectors may only signify that the process describes an arc in space of about 180 degrees and some sharp changes in direction would be expected RVP correlates with the voltage of S and S better with the larger of the two but best with the spatial sum of all S vectors. The sum is probably a better index of the total right ventricular forces than any single vector It is similar but not identical to the measurement previously described by Hugenholtz and associates as having the best correlation with RVI i.e the sum of the maximum

spatial vector to the right plus three other spatial vectors 5 msec before and 5 and 10 msec after it. The maximum S vector is usually the same as the maximum vector to the right.

The spatial voltage of the S vectors in pulmonary stenosis has a high degree of correlation with its projection on the fp (Fig. 6). This is not true in normal loops for S is almost directly posterior and its projection in the fp is minimal and inconstant. As S increases, however, its position shifts anteriorly thereby projecting more on the fp which therefore in a sense combines the two related variables (voltage and angular displacement). The correlation between S_3 and S_f is also improved by the growth of S along the Y axis.

The R vector is loosely labelled the left ventricular free wall vector but its position and voltage even in the normal must be modified by right ventricular depolarization. Its influence on R becomes evident in severe pulmonic stenosis for R is smaller and more anterior. The changing relationship between right and left ventricular mass is expressed in the VCG by the relative size of right and left forces (Max S_3/R). The correlation is, however, not as good as with the voltage of S alone indicating that changes in R are not as sensitive or consistent. The normal wide angle between S and R vectors in the hp is about 270 degrees but they tend to converge anteriorly as pressure increases. The direction of inscription of the R loops also roughly indicates RVP. With RVP less than 70 mm. Hg it was always counterclockwise. With pressures in the 70 to 100 mm. Hg range transcription was variable, but above 100 was always clockwise (Fig. 3). This description is almost identical to that of the Frank VCG but in contrast to that of the cube in which reversal of inscription occurs with minimal disease.

Prediction of RVP from VCG and ECG. The correlations between VCG measurements and RVP are surprisingly good considering the wide range of ages represented. The principal correlations, however, are with the angle and voltage of S. The angles of the principal vectors in this lead system are remarkably constant in normal patients from ages 7 to 39.[11] The voltages in children are higher than in adults but these differences are least striking for S.

There are obvious qualifications to the use of equations for predicting RVP which are based on VCG parameters. They are invalid in the presence of right bundle branch block. Extracardiac factors decreasing voltage such as pericardial effusion, anasorca, etc. will make voltage measurements useless but may not affect correlations dependent on angles. Ordinarily the multiple regression equation will give the most reliable estimate. In spite of the numerous calculations made in this study, exploration has not been complete. The best predictive equation, for example, might incorporate ECG, VCG, and certain phonocardiographic measurements known to correlate well with RVP.[12]

Clinicians ordinarily consider pressure loading in terms of RVP. It is therefore fortunate that the correlations are not improved by considering more complex derivations. There are reasons why one might expect the best correlations with RVP. Increased intramural tension has been suggested as a stimulus to hypertrophy.[13] In concentric hypertrophy, where chamber volume is not increased, according to the law of Laplace pressure is the only determinant of intramural tension. With relatively stable resting heart rates and flows, pressure will also be the main determinant of TTI. Furthermore, at least in acute experiments, increments of pressure work are metabolically more costly than those of flow. Therefore combining flow measurements with pressure in such expressions as "stroke work" or "valve area" would be a relatively unimportant addition. The physiological fluctuations of flow plus inaccuracies of measurement might only decrease the correlations obtained with pressure. This explanation is compatible with the data presented. Acceptable correlations have been reported between estimates of left ventricular mass and the voltage of vectors derived predominantly from this chamber. A logical assumption is that the voltage of the S vectors reflects right ventricular mass.

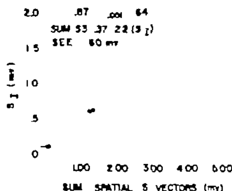


Fig. 7A. The S wave in Lead I closely correlated with the voltage of the S vectors on the vectorcardiogram.

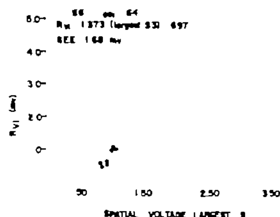


Fig. 7B. The R in V has the best correlation with any hemodynamic parameter (right ventricular stroke work). It is closely related to the largest S vector the vectorcardiogram.

Correlations with the ECG. The best correlations between the ten ECG indices of right ventricular overload and hemodynamic measurements appear in Table II. The best prediction of RVP was obtained with the voltage of S_I (r = 0.76) and was not improved by combination with the peak R voltage in V (r = 0.73). Attempts to find correlations between hemodynamic and ECG measurements reveal wide discrepancies even within the same laboratory. For example, Nadas has reported coefficients of correlation between R_{V1} and RVP of 0.5 and 0.78. The inconsistency suggests that the best correlations may be due to fortuitous sampling. The same suspicion about excellent VCG correlations can only be dispelled by further confirmations.

It is curious that the best ECG correlations are with the derived pressure flow expressions (TTI, SW). No physiological explanation is apparent and earlier reports are not universally confirmatory. At any rate, the expressions are more unwieldy than RVP and the VCG correlations are generally superior.

The two key ECG measurements (S_I, R_{V1}) reflect the same forces which give the high correlations between VCG and RVP. The best correlations between them and a VCG measurement is with the Max. S_s (r with S_I = 0.92, with R_{V1} = 0.87). This is hardly surprising in the case of R_V, which is principally a force in hp. S_I is mainly a fp projection but, as previously noted, in pulmonary stenosis the fp linearly reflects the spatial S voltage (Fig. 6). The correlations between S_I and R_{V1} and the most useful VCG measurements are expressed in Fig. 7.

Summary

The Helm sponge VCG lead system has been tested in a study of 21 patients with isolated pulmonary stenosis. Correlations between 7 hemodynamic, 70 VCG, and 10 ECG parameters have been scanned. From these, the best correlations have been presented and include 4 hemodynamic, 12 VCG, and 4 ECG measurements. Right ventricular peak pressure shows the highest correlation with VCG measurements. The best is with the spatial sum of the terminal (S) vectors (r = 0.90), but prediction of right ventricular pressure, particularly in severe stenosis, can be significantly improved by use of a multiple regression equation utilizing 3 VCG and 1 ECG variable (r = 0.94).

The development of the major changes of the QRS loop with concentric hypertrophy is seen to be a continuum gradually disclosing the activation sequence of the right ventricle. The S vector simultaneously increases its voltage, swings anteriorly, and occurs earlier. Changes in the R vector are not linearly related to increasing pressure over the entire range but are evident in the severe cases in which R becomes anterior earlier, smaller, and may disappear completely.

REFERENCES

1. Gamboa, R., Hugenholtz, P. G. and Nadas, A. S. Corrected (Frank) uncorrected (cube) and standard electrocardiographic lead systems in recording augmented right ventricular forces in right ventricular hypertension, Brit. Heart J. 28:62, 1966.
2. Fischmann, E. J. Experimental comparison of parallel grid leads with simple bipolar and the SVEC III, Frank, and McFee-Parungao systems. II. Transverse and vertical leads, Am. Heart J. 70:627, 1965.
3. Brody, D. A. and Arzbaecher, R. C. A comparative analysis of several corrected vector cardiographic leads, Circulation 29:533, 1964.
4. Helm, R. A. An accurate lead system for spatial vectorcardiography, Am. Heart J. 53:415, 1957.
5. Witham, A. C. The vectorcardiogram recorded with sponge electrodes, Am. Heart J. 72:730, 1966.
6. Witham, A. C. Quantitation of the vector cardiogram, Am. Heart J. 72:284, 1966.
7. Sarnoff, S. J., Braunwald, E., Welch, G. H., Jr., Case, R. B., Stainsby, W. N. and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index, Am. J. Physiol. 192:148, 1958.
8. Helm, R. A. Vectorcardiographic notation, Circulation 13:581, 1956.
9. Scher, A. M. The sequence of ventricular excitation, Am. J. Cardiol. 14:287, 1964.
10. Boineau, J. P., Spach, M. S., and Ayers, C. R. Time-normalized correlation of ventricular activation and the vectorcardiogram, Am. Heart J. 73:64, 1967.
11. Witham, A. C. Sponge vectorcardiogram in children, Am. Heart J. (In press).
12. Gamboa, R., Hugenholtz, P. G. and Nadas, A. S. Accuracy of the phonocardiogram in assessing severity of aortic and pulmonic stenosis, Circulation 30:35, 1964.
13. Badeer, H. S. The stimulus to hypertrophy of the myocardium, Circulation 30:128, 1964.
14. Hugenholtz, P. G. and Ellison, R. C. Clinical assessment of left ventricular weight, Circulation (Suppl. III) 34:131, 1966 (Abstr.)

Experimental and laboratory reports

The contrasting effects of diphenylhydantoin and procaine amide on A V conduction in the digitalis-intoxicated and the normal heart

Benjamin J. Scherlag, Ph.D.
Richard H. Helfant, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

Two important effects of digitalis excess are known to be the production of ectopic rhythms and a prolongation of A-V conduction. Although this latter property is of use clinically to slow the ventricular rate in atrial flutter or fibrillation, a frequent manifestation of digitalis excess is A-V block of varying severity.[1] One of the major problems associated with those agents most commonly used to treat digitalis-induced ventricular arrhythmias is their tendency to exacerbate the A-V conduction abnormality produced by the glycoside. Recently, several investigations have reported that diphenylhydantoin (DPH) is an effective agent in counteracting ventricular ectopic activity produced by digitalis. The purpose of this study is to compare the effects of DPH and procaine amide on A-V conduction in the digitalis-intoxicated and the normal heart.

Methods and materials

Intravenous sodium pentobarbital (30 mg. per kilogram) was administered to 26 adult mongrel dogs weighing 13 to 20 kilograms. Under controlled ventilation a thoracotomy was performed at the right fourth intercostal space and the heart exposed through a pericardiotomy. Two pairs of fine Teflon-coated wires were inserted into the right atrium. For pacing purposes, one of these pairs was placed at the tip of the atrial appendage. The atrium was paced at a fixed rate (200 per minute) by impulses of 2.5 msec. duration delivered from an AEL Stimulator and Isolation Unit at 20 per cent above threshold intensity. The other pair of wires was inserted into the posterior wall of the atrium in the region of the common bundle in order to obtain a His bundle electrogram—a technique that has been described in previous reports.[7] Lead II of the standard electrocardiogram (ECG) was also recorded. Blood pressure was monitored through a catheter in the femoral artery. All records were taken at low (25 mm. per second) and high (200 mm. per second) speeds on a photographic oscilloscopic recorder.

After control tracings were recorded, intravenous acetylstrophanthidin (7.5 µg

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
Supported in part by Division of Direct Health Services, Bureau of Health Services, United States Public Health Service Project Nos. Py 7-46 and Py 7-49.
Received for publication March 13, 1967.

per kilogram injection and 3 0 μg per kilogram per minute infusion) was given until a stable ventricular tachycardia occurred If untreated the acetylstrophanthidin-induced ventricular tachycardia persisted for 30 to 45 minutes due to the cumulative effects of the infused glycoside. However intravenous DPH (5 mg per kilogram) or procaine amide (15 to 30 mg per kilogram) was then administered to convert the ventricular tachycardia to regular sinus rhythm. High speed records (200 mm per second) were taken every 2 to 5 minutes throughout each experiment A V conduction time was determined as the interval from the beginning of the P wave to the His bundle deflection during regular sinus rhythm and atrial pacing In seven separate studies, the effects of DPH (5 mg per kilogram) or procaine amide (30 mg per kilogram) alone on A V conduction time were determined.

Results

Table I indicates the comparative effects of DPH and procaine amide on A V conduction time in the digitalis-intoxicated heart. Acetylstrophanthidin consistently caused a prolongation of A V conduction time during regular sinus rhythm (average 46 per cent) This effect was also evident at constant heart rates during atrial pacing at 200 per minute (Table I Exps. 9 and 10) The administration of DPH (5 mg per kilogram) invariably converted the acetylstrophanthidin induced ventricular tachycardia to regular sinus rhythm and in every case A V conduction time returned to control values within 15 minutes. In experiments 1 3 6 and 8 (Table I) the restoration of nor

Table I The effects of DPH o procaine amide on A V conduction in the digitoxic heart

Exp	Control A V conduction			Digitalis toxicity A V conduction			Conversion A V conduction		
	HR	RSR	RAP†	HR	RSR	RAP†	HR	RSR	RAP†
A DPH (5 mg per kilogram)									
1	150	50	—	160	60	—	150	48‡	—
2	215	53	—	220	85	—	210	53	—
3	150	74	—	150	140	—	150	74‡	—
4	150	66	—	160	125	—	160	66‡	—
5	125	58	—	80	2°HB	—	130	58	—
6	160	55	—	155	76	—	155	55	—
7	170	70	—	160	105	—	160	65	—
8	140	61	—	140	92	—	140	61‡	—
9	168	62	67	110	120	2°HB	165	63	65
10	175	55	76	162	76	93	175	55	60
Average		60 ± 9			98 ± 25 p < 0.001			59 ± 7 p < 0 001	
B Procaine amide (30 mg per kilogram)									
11	150	55	—	160	65	—	125	115	—
12	180	70	—	180	87	—	120	110	—
13	140	78	—	140	93	—	115	110	—
14	125	49		120	—	—	Cardiac arrest		
15	150	5	—	150	—	—	135	98	—
16	150	50	55	140	62	93	120	76	130
Average		61 ± 11			77 ± 16 p < 0 05			102 ± 15 p < 0 05	

Exp experiment number HR heart rate RSR A-V conduction time during regular sinus rhythm (msec) RAP A-V conduction time during right atrial pacing (msec) 2°HB 2° A-V block.
A-V conduction times and rates tabulated were those taken 5 minutes after conversion.
†All paced rates, 200 per minute
‡Restoration of control A-V conduction time occurred 2 to 3 minutes after conversion.

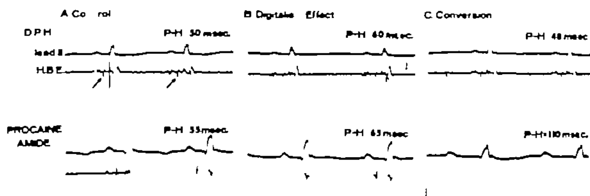


Fig. 1. The effect of DPH and procaine amide on A-V conduction in the digitoxic heart. Top tracing, standard Lead II of ECG lower tracing, His bundle electrocardiogram (H B E.) A V conduction time P et His bundle terval (P H). *A* Control top record P H = 50 msec. bottom record P H = 55 msec *B* Acetylstrophanthidin administration causes an increase in P H intervals. *C* DPH conversion of acetylstropha thidin tox ict results in decrease in P H i terval to 48 msec Procaine amide con ersion however results in further prolong tion of P H t 110 msec.

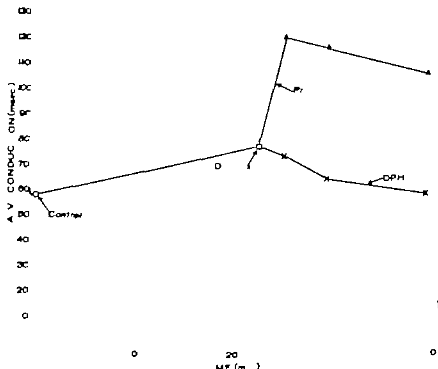


Fig. 2 A graphic representation of the compar tiv effects of DPH nd procaine amide (PRO) on A V conduction after conversion of digitalis toxicity Prior t the onset of entricular tachycardia induced by acetylstrophanthidin, there is a 46 per cent increase in A V conduction time abov control. DPH con ersion of d talis toxicity reverts A V conduction to erage control values whereas procaine amide conversion further increases the A V conduction prolongation caused by the glycoside

mal A V conduction occurred in less than 5 minutes after the administration of DPH A typical case is illustrated in Fig 1

Procaine amide (15 to 30 mg per kilogram) converted the acetylstrophanthidin-induced ventricular tachycardia in 5 of 6 cases. In each study in which conversion occurred there was a consistent prolongation of A V conduction time during regular sinus rhythm (average 39 per cent) above the A V conduction delay caused by the glycoside alone This effect occurred immediately after the administration of procaine amide and persisted with little diminution for more than two hours. A graphic representation of the effects of DPH and procaine amide on A-V conduction in the digitalis-intoxicated heart is shown in Fig 2

The effects of DPH (5 mg per kilogram) and procaine amide (30 mg per kilogram) on the undigitalized heart are shown in Table II Whereas DPH had no effect in three cases, there was a decrease in A V conduction time in three other experiments. The average decrease was 7 1 per cent In four cases, procaine amide (30 mg per kilogram) caused slowing of A V conduction (average 20 per cent)

Discussion

The findings of the present study indicate that DPH completely reverses the A V prolongation caused by digitalis. Significantly with the same dose necessary to convert the acetylstrophanthidin-induced ventricular tachycardia to normal sinus rhythm DPH restored A V conduction to normal values. In the nondigitalized heart, diphenylhydantoin produced no change in some cases or a slight decrease in A V conduction time. It is significant that in the nondigitalized and digitoxic heart DPH actions were quantitatively different. Whereas DPH decreased A V conduction an average of only 7 1 per cent in the nondigitalized heart, it consistently reversed a marked increase in A V conduction (average 46 per cent) produced by digitalis excess. In two cases (Exps. 1 and 7 Table I) there was a slight reduction in A V transmission times below control values.

Conversely procaine amide consistently

Table II The effects of DPH or procaine amide on A V conduction in the nondigitalized heart

Exp	Control A V conduction			A V conduction		
	HR	*RSR*	*RAP*†	*HR*	*RSR*	*RAP*
A DPH (5 mg per kilogram)						
1	160	67	—	150	67	—
2	140	100†	—	140	100	—
3	180	71	—	180	63	—
4	160	78	—	160	72	—
5	175	60	63	170	60	62
6	190	50	50	190	38	40
Average 65 ± 12					60 ± 15	
B Procaine amide (30 mg per kilogram)						
7	140	87	—	103	101	—
8	-40	49	—	120	65	—
9	140	53	—	108	65	—
10	170	32	58	150	59	75
Average 61 ± 17					73 ± 19	

See footnote to Table I.

*After either D[illegible] or procaine amide A-V conduction times and heart rates listed were taken after 5 minutes.

†This value was not used in determining average, since the value is more than three standard deviations from the mean value for all controls.

The atrioventricular conduction tissue of the dog

Histochemical properties; influence of electric shock

Ronald Isaacson M.D
*Robert J Boucek M D***
Miami Fla

From morphologic, physiologic, and perhaps, embryologic considerations [1-4] the cells of the cardiac conduction system differ from surrounding myocardial cells. Because of these differences, it might be expected that these cells would have distinguishing metabolic properties as well It became the purpose of a series of investigations to examine, by histochemical techniques, the cells of the conduction tissue of the dog The histochemical techniques were selected in order to reflect the anaerobic and aerobic metabolic pathways the pentose phosphate shunt and the acetylcholine-acetylcholinesterase activity These studies indicate that the conduction system in the dog has unique histochemical properties when compared with atrial and ventricular muscle. And furthermore these metabolic properties are altered by electric shock and hypoxia.

Materials and methods

Ten randomly selected male and female mongrel dogs, on no previous drugs, were used in these experiments. Each dog weighing approximately 10 kilograms was premedicated intraperitoneally with 5 mg per kilogram of morphine sulfate. About 20 minutes later 500 mg per kilogram of chloral hydrate dissolved in 15M NaCl was given intravenously An electrocardiograph (ECG) machine was then connected to an adapter of a defibrillator apparatus so that continuous records could be obtained The defibrillator was, in turn connected to the animal

Four dogs were used as controls. Two of the remaining dogs were given three 100 watts per second electric shocks intermittently across a closed chest. The four remaining dogs were put into ventricular fibrillation two were put to death painlessly immediately after ventricular fibrillation was induced while the other two were defibrillated with electric shocks of moderate intensity

In each dog the chest was rapidly opened and the heart removed The heart was placed in gauze soaked in cold saline and dissected within 5 minutes. The right side of the heart was opened and a block of tissue (Fig 1) removed the block included

Supported in part by Public Health Service Training Grant No. HTS 5465 from the National Heart Institute N United Institutes of Health General Research Grant, H 5190 R; and Summer Research Fellowship from the Florida Heart Association.
Received for publication March 6, 196[illegible]
Medical School—Summer Research F llow University of Miami School of Medicine, Miami, Fla.
**From the Division of Cardiology Department of Medicine University of Miami School of Medicine and the Howard Hughes Medical Institute, Laboratories for Cardiovascular Research, Miami, Fla.

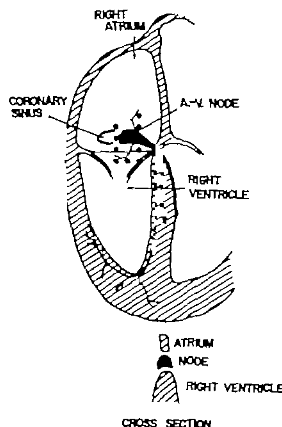


Fig. 1. Coronal representation of the dog heart showing the (dotted lines) resected area used for histochemical studies. Insert at the bottom reveals the tissue orientation used for sectioning.

right atrial and ventricular muscle and the A-V node and/or bundle.

This block of tissue was then mounted for fresh frozen sections in a polyvinyl pyrrolidine-gelatin mixture (2.5:1) and quick frozen on a bed of crushed dry ice. Each block was mounted and cut on a cryostat at a temperature of 20° C. at a thickness of 10μ. The tissue sections were placed on coverslips and then incubated in various media.

The following enzyme systems were studied: Succinic dehydrogenase (SDH), lactic dehydrogenase (LDH), glucose-6-phosphate dehydrogenase (G-6-PDH), and acetylcholinesterase (AChE) after the methods of Nachlas and associates, Hess and associates,[8] and Gomori.[9] The incubation conditions are listed in Table I. After incubation, all tissues were mounted in glycerin-gel, studied, and photographed under a light microscope. The intensities of the reactions were rated on an arbitrary I to IV basis.

Results

The intensities of the reductases, SDH, LDH, and G-6-PDH, as well as AChE (Figs. 2, 3, and 4) differ in the ventricular, atrial, and conduction cells of the dog heart. Of the three reductases, the greatest variation between tissues occurred with suc-

Table I

Enzyme system	*Substrate*	*Cofactors*	*pH*	*Incubation time*	*Temperature (°C)*	*Final reaction product and color*
Succinic dehydrogenase	Succinate	NAD, FAD, FMN	7.6	10 min.	37	Reduced salt-formazan (dark blue→black)
Lactic dehydrogenase	Lactate	NAD, NaAzide	7.2	20 min.	37	Reduced salt-formazan (dark blue→black)
Glucose-6 phosphate dehydrogenase	Glucose-6 phosphate	NADH, NaAzide, NaF	7.6	1 hr	37	Reduced salt-formazan (dark blue→black)
Acetylcholinesterase	Myristyl choline	CoAc, $CaCl_2$, $MgCl_2$, $MnCl_2$	7.6	1 h	37	Cobalt sulfide precipitate (black)
	Acetyl thiocholine	Copper sulfate, $MgCl_2$, maleic acid	0	1 h	37	Copper sulfide precipitate (brown)

The following abbreviations are used: NAD and (H): Nicotinamide adenine dinucleotide and reduced form; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; NaAzide, sodium azide; NaF, sodium fluoride; CoAc, cobalt acetate. Others are standard chemical designations.



Fig [illegible] Enzyme react[illegible] the [illegible] m (1) [illegible] entricular [illegible] tissue (C) and [illegible] entricle (1) (*1*) succl [illegible] dehydrogenase (*2*) lactic dehydrogenase and (*3*) gluc [illegible] phosphate dehydrogenase [illegible] the tissue [illegible] responsible for the [illegible] lines seen [illegible] *1* and *2* (×25)

cinate and lactate and the least with glucose-6-phosphate as substrates. AChE was confined almost exclusively to the conduction tissue.

An intense SDH reaction and a somewhat less intense LDH reaction occurred in the ventricular muscle when compared with the atrial tissue (Fig 2,*A*) The reactions were intense over the cross striations (Fig 6) and along the cell borders, with no unusual localization over the intercalated discs. The LDH was more prominent, while the SDH was less intense in the atrial than in the ventricular cells (Fig 2 *I*) The localization of the reaction in the atrial cells was similar to that observed in the ventricular cells. G-6-PDH was equally reactive in the atrium the ventricle and the conduction system (Fig. *2 C*) The conduction system was unique with a weak SDH reaction and an LDH reaction which was extraordinarily prominent the latter reaction exceeding in intensity the reaction seen in the atrium and ventricle (Fig 3 solid bar in the columns to the left in the middle panel)

Another distinguishing histochemical feature of the conduction tissue area was the AChE reaction (Fig 3 lower panel columns to the left of the figure) Because of the heavy localization of nerve elements in this region efforts to distinguish between *the enzyme elements of the conduction* and the nerve tissues were made by using two substrates myristyl choline and acetyl thiocholine (Fig 4) With myristyl choline the reaction was intense and diffusely distributed over the conduction tissue Acetyl thiocholine gave a less intense reaction and the location of the reaction was, in general similar to that seen with myristyl choline With both substrates, a zone of high activity surrounded the bundles of conduction tissue

Electroshock experiments A group of animals was given three electric shocks of 100 watts per second across the closed chest The timing of the electric shocks was such that ventricular fibrillation was not induced and only transient tachycardia occurred Following the electric shock the intensity of the SDH reaction was reduced in each of the three tissues while the LDH reaction was increased (Fig 3 middle

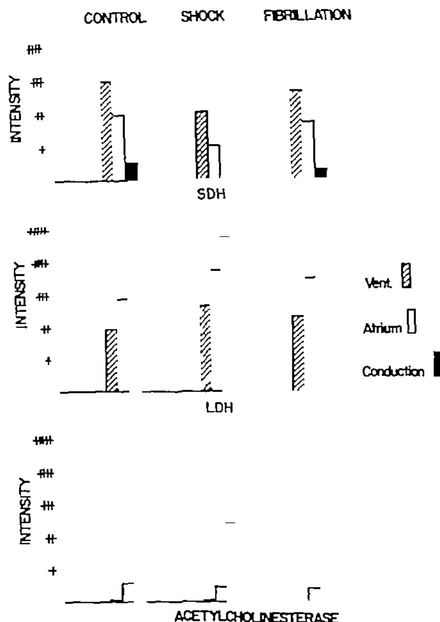


Fig. 3. The intensities of the succinic and lactic dehydrogenase and the acetylcholinesterase in the three tissues with electroshock (200 watt per second), middle columns, and with ventricular fibrillation, columns to the right, to be compared with the control tissue columns to the left.

panel columns to the left of the figure). In the atrioventricular node the AChE reaction was reduced while the reaction around the tissue bundles was prominent.

Ventricular fibrillation—myocardial ischemia. Ventricular fibrillation was induced in a group of dogs by interdicting a 7 watts per second electric shock with the peak of the T wave of the electrocardiogram. In these animals the SDH was slightly reduced while the LDH was intensified over the atrial and ventricular cells. The AChE intensity was slightly reduced in the conduction tissue cells (Fig. 3, column of bars to the right in the figure).

Ventricular fibrillation plus electric shock conversion. Two of the dogs were placed

Fig. 4. Acetylcholinesterase reactions in the conduction tissue with (*1* and *2*) myristyl choline and (*3* and *4*) with acetyl thiocholine as substrates. Note the intense reaction around the muscle cells. (1 and 3 ×25; 2 and 4 ×376.)

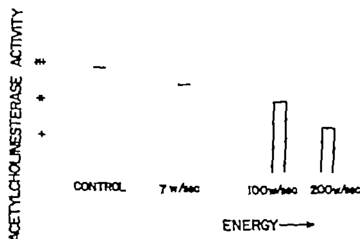


Fig. 5. A comparison of the intensity of the acetylcholinesterase reaction in the conduction tissue following electroshocks of different magnitudes.

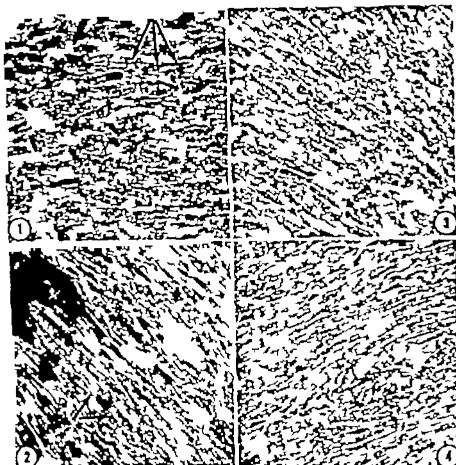


Fig 6 Alteration of the cytologic appearance of the dehydrogenase reactions in the ventricular muscle cells following short interval of electroshock induced ventricular fibrillation. Note the orderliness of the fine formazan deposits along the cross striations arrow in the control (Fig 1), while in electroshock plus ventricular fibrillation the formazan material aggregates along the cell margins or over the nuclei, arrow in Fig 2. A similar although less drastic change is seen with the lactic dehydrogenase reaction, 3 vs 4 (×564.)

in ventricular fibrillation and then converted to sinus rhythm with either a 100 or a 200 watts per second electric shock. The animal receiving the 100 watts per second electric shock had SDH and LDH changes in the atrium and ventricle similar to those described for the animals receiving three electric shocks across the closed chest. However in the animal receiving the 200 watts per second electric shock, both the SDH and LDH were reduced in intensity A marked reduction in the intensity of SDH and the AChE activity of the conduction tissue was seen in these animals.

Comparing the intensity of AChE reaction in all experimental conditions in which electroshock was used, there seemed to be an inverse relationship between the energy of the electric shock and the intensity of the reaction (Fig 5) Electric shocks of 200 watts per second nearly eliminated the reaction over the cells of the conduction system.

Certain common changes were seen in cytologic features of the SDH LDH and AChE reactions following electroshock or fibrillation. In the tissue from the control animals, the formazan or cobalt precipitates were aligned along the cross striations of the muscle cells (Fig 6) whereas following electroshock or fibrillation, the precipitates seemed to accumulate along the cell borders or over a cellular organelle

Cytologic and electrocardiographic correlations The most drastic changes in the morphology of the conduction system oc

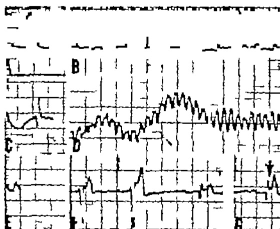


Fig. 7. Standardization (A), control (B), electroshock (C) and ventricular fibrillation (D). E, F, conversion with 200 watt per second electric shock to sinus rhythm. G, note the S-T segment elevation and the shortening of the QT interval.

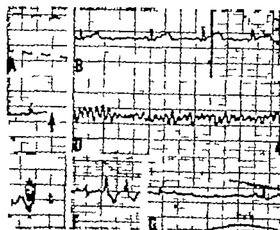


Fig. 8. Continuous electrocardiographic monitoring of dog with induced ventricular fibrillation. A, and B, control record with standardization. C, electroshock with the T (arrow) followed by D, ventricular fibrillation. E, electroshock (100 watts per second). F, immediate ventricular response. G, minor degrees of A-V conduction disturbance just prior to death.

curred following defibrillation with 200 watts per second electric shock and were characterized by a marked reduction of the SDH and the AChE reactions. A reduction in the intensity of SDH in the ventricular myocardial cells was also seen. In these animals, a prolongation of the atrioventricular conduction time, a shortening of the QT interval, or some elevation of the S-T segment (Fig. 7) was seen on the electrocardiogram. Electric shocks of 100 watts per second associated with less intense histochemical changes in the conduction system and in the ventricle had minor degrees of A-V conduction disturbance, a shortening of the QT interval and some displacement of the S-T segment (Fig. 8).

Discussion

These results indicate that the cells of the cardiac conduction system do have unique histochemical properties. These differences are clearly illustrated when the reactions with succinate and lactate are compared in the conduction system and in the myocardial cells. Additional and striking differences between the two cell types are seen with the AChE stain.

Variations in the intensity of the dehydrogenase reaction in cardiac tissue may provide insights into the relative prominence of various metabolic pathways in the different cells at that particular time. For example, an intense succinic dehydrogenase, an enzyme requiring oxygen to catalyze the conversion of succinate to fumarate, implies a conspicuous aerobic metabolism for the cells, while a highly active lactic dehydrogenase enzyme, a component of the anaerobic glycolytic pathway catalyzing the oxidation of lactic to pyruvic acid, may reflect a prominent potential for anaerobic activity. Using this criterion it follows that the ventricular cell differs from the cell of the conduction system by its greater aerobic activity, and this deduction seems to be supported by Schreiler's observation of a low oxygen consumption by the conduction tissue.

Embryologists[3,7] have suggested that the conduction tissue resembles the cells of the embryonic heart, and some of the subcellular characteristics of the conduction tissue cells, i.e., the desmosome attachment between cells, the infrequent mitochondria, and the poorly developed myofibrils,[12] support this possibility. Our findings of a relatively prominent G-6-PDH in the conduction cells (when contrasted with the SDH reaction) and an intensely active LDH reaction would suggest that the conduction tissue may have biochemical

characteristics resembling those reported for fetal cardiac cells as well. Jolley and associates[12] observed a lower glucose oxidative ability in the fetal tissue when compared to the heart tissue of the adult animal. In addition, they reported that the concentrations of pentose cycle enzymes are higher and the reactions that they catalyze are greater in fetal than in the adult tissue. Beatty and co-workers[3] report similar findings in the fetal rhesus monkey.

Conduction tissue is distinguishable in the adult heart by a prominent AChE activity. Recently we suggested that the atrioventricular pause (P-R interval) in the transmission of the depolarization process in the preneural embryonic heart may be due to a high concentration of AChE[7] along the atrioventricular junction. Lieberman and Paes de Carvalho[1] reported action potentials along the entire atrioventricular juncture of the 72-hour chick embryo heart (preneural at this stage) comparable to those seen in the adult rabbit atrioventricular nodal tissue.

The conduction tissue in the adult animal includes a heavy cholinergic innervation which in itself contains a high level of AChE activity. Boeke[14] demonstrated many years ago that each cell of the atrioventricular is richly innervated and recent electron microscopic studies of the conduction tissue indicate the presence of synaptic vesicles in these neurons.[15] As a result, it is not possible to say without qualification that the histochemical evidence of intense AChE activity in the A-V node area indicates a concentration of AChE within the cells of the conduction tissue.

Electrocardiographic changes induced by electric shocks provide some basis for correlation between morphologic features and cellular function. It was observed that a prolongation of the atrioventricular conduction time occurred in dogs receiving an electric shock of 200 watts per second. The A-V nodal tissue of these dogs had no demonstrable AChE over the cell body but only a concentrated reaction around the muscle cells. In the preneural chick embryo heart supplemental AChE also prolonged the P-R interval of the electrocardiogram. In these preneural embryo hearts the supplemental AChE must have exerted an action along the cell border since diffusion of the large enzyme molecule through the cell membrane into the cell would be unlikely. Perhaps the rate of transmission through the A-V node is determined in part by the concentration of AChE in or on the cell membranes of the conduction tissue.

Another correlation between the cytologic findings and functional properties may exist in the presence of a shortened QT interval noted in the electrocardiogram in dogs receiving 100 watts per second electric shocks. In these dogs, cytologic changes occur in the location of the intracellular enzymes from an orderly pattern of reductases along the cross striations of the muscle cell to aggregates of enzyme activity along the cell border or over organelles. This translocation of enzyme activity suggests a disturbance in the hierarchy of the enzyme elements of the cell which may influence the repolarization process underlying the QT interval of the electrocardiogram.

Electric shock reduces the intensity of the SDH while increasing the intensity of LDH in the cells of the atrium, ventricle, and conduction tissue (Fig. 3). Electroshock might have reduced the aerobic metabolic activity while increasing the anaerobic activity. If this reaction is common for myocardial injury in general, then from teleogical considerations such an adaptability would permit the continued generation of energy, albeit less efficient, in the presence of tissue damage.

Summary

The atrioventricular conduction tissue of the dog has distinguishing histochemical properties, the most remarkable of which are the prominent staining reactions for acetylcholinesterase and lactic dehydrogenases. A weak succinic dehydrogenase staining reaction occurs in the conduction tissue. Electric shocks cause a reduction in the intensity of the acetylcholinesterase and succinic dehydrogenase reactions and an intensification of the lactic dehydrogenase reaction. Some functional correlations are drawn between the altered histochemical reactions and electrocardiographic alterations following electric shocks.

REFERENCES

1. Keith A., and Flack M. The form and nature of the muscular connections between the primary divisions of the vertebrate heart, J Anat. Physiol. 41 172, 1906.
2. Tawara, S. Das reizleitungssystem des Saugetierherzens, Gustav Fischer Jena, 1906, in Robb, J S and Petri R. Expansions of the atrio-ventricular system in the atria, in Paes de Carvalho, A De Mello, C W and Hoffman, B F editors The specialized tissues of the heart, Amsterdam The Netherlands 1961 Elsevier Publishing Company p. 1.
3. Purkinje, J Mikroskopisch-neurologische Beobachtungen, Arch Anat Physiol. u. Wiss. Med. 12:281 1845
4. Hoffman, B F Paes de Carvalho, A., and De Mello, W C Electrical activity of single fibers in the A V node, Nature 181:66, 1958.
5. Patten B M The development of the sinoventricular conduction system, Univ Mich. Med Bull 22 1 1956.
6. DeHaan R. L Regional organization of pre-pacemaker cells in the cardiac primordia of the early chick embryo J Embryol. & Exper Morphol 11:65, 1963
7. Nachlas, M M Tsou K C Souza, E De, Chang C S and Seligman, A M Cytochemical demonstration of succinic dehydrogenase by the use of a new p-nitrophenyl substituted ditetrazole J Histochem & Cytochem 5:420 1957
8. Hess, R Scarpelli, D G and Pearse A. G E. The histochemical localization of oxidative enzymes II Pyridine nucleotide-linked dehydrogenases, J Biophys & Biochem Cytol 4 753 1958
9. Gomori, G Microscopic histochemistry Chicago, 1952 Chicago University Press, p. 209
10. Schiebler T H on Neuere vor teilungen om Umbau des Myokards nd des Reizleitungssystems, Muenchen. Med. Wchnschr 103 1 1961
11. Robb, J S., and Petri, R. Expansions of the atrio-ventricular system in the atria, Paes de Carvalho, A. De Mello, C. W and Hoffman, B F editors: The specialized tissues of the heart, Amsterdam The Netherlands, 1961 Elsevier Publishing Company p. 1
12. Rhodin, J A. G: An atlas of ultrastructure, Philadelphia, 1963, W B Saunders Company p. 32
13. Leak, L. V and Burke, J F The ultrastructure of human embryonic myocardium Anat Rec. 149:623 1964
14. James, T N Sherf L., Fine G., and Morales, A. R. Comparative ultrastructure of the sinus node in man and dog, Circulation 34 139 1966.
15. Jolley R L., Cheldelin V H., and Newburgh, R. W Glucose catabolism in fetal and adult heart, J Biol. Chem. 233 1289 1958.
16. Beatty C. H Basinger G M and Bocek R. M Pentose cycle activity in muscle from fetal, neonatal and infant rhesus monkeys, Arch. Biochem. & Biophys. 117:275 1966.
17. Carbonell, C M Esterases of the conduction system of the heart, J Histochem. & Cytochem. 4:87 1956.
18. Paff G H Boucek, R. J and Glander T P Acetylcholinesterase-acetylcholine an enzyme system essential to rhythmicity in the preneural embryonic chick heart, Anat. Rec. 154:675 1966
19. Lieberman, M and Paes de Carvalho, A.: The electrophysiological organization of the embryonic chick heart, J Gen. Physiol. 49:351 1965
20. Boeke J The innervation of the muscle-fibers of the myocardium and of the atrioventricular bundle of His in the heart of the tortoise (emys and cyclemys) Proc. Akad. Van Wetens. Sec. of Science 28:35, 1925
21. Torii, H Electron microscope observations of the S-A and A V nodes and Purkinje fibers of the rabbit, J p Circ. J 26:39 1962

Influence of calcium on myocardial potassium balance, oxygen consumption, and performance

J. P. Gilmore, Ph.D.
W. M. Daggett, M.D.
R. H. McDonald, M.D.
S. J. Sarnoff, M.D.
Bethesda, Md.

Although calcium has long been known to be intimately related to the contractile events in cardiac muscle, recent work in contraction coupling has increased interest in the role of ionized calcium in myocardial energetics. Recent work in this laboratory has shown that marked changes in myocardial function are attended by changes in myocardial potassium balance and, in addition, that changes in myocardial function are not necessarily accompanied by changes in oxygen consumption.[1-8] In order to understand more fully the mechanisms by which calcium influences the performance of the heart, experiments were undertaken to determine the changes in oxygen consumption and myocardial potassium balance that accompany the inotropic effects of this cation. These experiments have been reported briefly elsewhere.

Methods

The modified isolated supported heart preparation was employed in all experiments. In this preparation, blood enters the left atrium from a reservoir through a variable resistance and flowmeter, leaves the left ventricle and proximal part of the aorta through a second resistance and returns to the reservoir. The left coronary artery is perfused from a second reservoir at constant pressure (approximately 80 mm Hg) through a Gregg coronary cannula. The left coronary artery reservoir, which contains at any given time approximately 800 ml. of blood, receives its blood by a pump from the atrial reservoir. In this preparation, the right coronary artery is supplied by the aorta. Total coronary outflow is led from the pulmonary artery and through a rotameter to a reservoir connected to the jugular veins of a second dog. Blood is then led at a rate which approximates the total coronary outflow of the isolated heart from the cannulated femoral arteries of the support dog to the reservoir which supplies blood to the left atrium of the isolated heart.

Continuous samples of left coronary arterial and coronary venous blood are passed through a Guyton A-V O_2 analyzer and then to the support dog reservoir. The output of the analyzer is used as an indicator of a steady state and as a check on the A-V O_2 differences determined on individual samples by the method of Van Slyke and Neill.

From the Laboratory of Cardiovascular Physiology, National Heart Institute, National Institutes of Health, Bethesda, Md.
Received for publication March 27, 1967.
Address: Department of Physiology, University of Virginia, Charlottesville, Va.

Left ventricular pressure was measured with Statham transducers through a short wide-bore Y-shaped metal cannula inserted through the apical dimple: one transducer recorded the full left ventricular pulse and the other recorded left ventricular pressures from 0 to 40 cm. H_2O. Aortic pressure was recorded from a cannula introduced through the right common carotid artery into the aortic arch and connected directly to a Statham transducer. The first derivative of the left ventricular pulse (dp/dt) was recorded and calibrated by a linear sawtooth voltage. Cardiac inflow was automatically maintained by an electronic valve control system. Duration of systole was calculated as the time from the beginning of ventricular systole to the dicrotic notch of the aortic pressure recording.

Heart rate was controlled by a Grass impulse generator through a bipolar electrode sutured to the right atrial appendage. Clotting was prevented by an initial dose of 5 mg. per kilogram of heparin and an hourly dose of 20 mg. to both the support dog and the main reservoir.

Calcium chloride was infused directly into the left coronary artery inflow line. The solution used contained 100 mg. of calcium chloride per milliliter of distilled water.

Coronary arterial and venous blood samples for plasma K^+ analysis were obtained from the coronary inflow and outflow lines, respectively. Arterial samples were obtained distal to the site of infusion of calcium chloride. Determinations of hematocrit were done on arterial and venous samples. The analysis of plasma K^+ was done using a Technicon autoanalyzer. Net K^+ flux was calculated as the product of the change in the coronary arteriovenous difference and coronary plasma flow. In this preparation the right coronary artery is supplied by the aorta. Arterial K analysis was made only on blood perfusing the left coronary artery. Stability of the left coronary artery plasma K^+ concentration, however, indicates stability of the right coronary arterial plasma K^+ since both receive their inflow from the same source. For all experimental runs, simultaneous coronary arterial venous sampling was begun in the control period and continued during the period of calcium infusion.

Results

The data to be presented were obtained from 11 experiments which were done on six isolated supported hearts.

Influence of calcium on ventricular dy-

Table I. Cardiac effects of calcium chloride

Exp. No.	I. f. rat (mg./m.)	Heart rate		A.P. (mm. Hg)		LVEDP (cm. H_2O)		Max dp/dt (mm. Hg/sec.)		D.S. (msec.)	
		C	I	C	I	C	I	C	I	C	I
1	110	171	143	55/18	81/10	42.0	18.0	—	—	—	—
2	50	185	185	74/32	60/20	21.5	9.0	650	750	200	200
3a	30	166	166	145/40	145/30	30.0	7.0	1,700	2,400	240	195
3b	13	166	166	188/108	181/105	34.0	14.0	2,400	2,600	225	205
3c	57	171	171	173/115	175/112	24.0	10.0	1,600	3,100	225	185
3d	120	166	166	186/120	195/115	23.0	10.5	1,950	2,600	220	175
4	120	167	167	170/100	157/95	22.0	9.0	2,300	4,050	235	210
5a	14	136	136	173/108	169/107	43.0	12.0	1,500	1,650	280	275
5b	53	133	133	166/105	167/107	33.0	13.0	1,450	1,800	290	270
5c	5.6	140	140	136†	136†	29.0	23.0	1,650	1,750	—	—
6	50	152	152	60/30	72/32	30.0	18.0	600	800	—	—

*C, control; I, during $CaCl_2$ infusion; Inf. rate, infusion rate; AP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; max dp/dt, first derivative of left ventricular pressure; D.S., duration of systole; D. eject., duration of ejection; MVO_2, myocardial oxygen consumption; CI, cardiac input; TCF, total coronary flow; TTI, tension time index.

†Mean aortic pressure.

namics With heart rate stroke volume, and aortic pressure held relatively constant, infusion of calcium chloride into the left coronary artery was always associated with a lowering of left ventricular end-diastolic pressu e an increase in dp/dt a decrease in the duration of ejection, and in most experiments, a shortening of the time of total systole (Table I) A tracing from a typical experiment is shown n Fig 1 The panel on the left (*A*) shows dynamic tracings obtained during the control per od The middle panel (*B*) shows a slow speed tracing obtained at the beginning (arrow) of the infusion of 50 mg per minute of CaCl The small transient increase in mean aortic pressure shown in this panel occurred before aortic resistance was ad justed in order to ma ntain mean aortic pressure constant The right panel (*C*) shows a high-speed tracing obtained during the calcium infusion. At constant aortic pressure, card ac output and heart rate, left ventricular diastolic pressure (LVDP) declined 14 0 cm. H_2O dp/dt increased 500 mm. Hg per second the duration of ejection decreased 20 msec and the dura tion of total systole decreased 40 msec.

Influence of calcium on cor nary blood flow and myocardial oxygen consumption In the 11 experimets done, calcium in creased coronary blood flow in 6 decreased it in 2 and produced no significant change in 3 (Table I) There was no consistent correlation found between changes in contractility and changes in coronary blood flow as a function of infusing $CaCl_2$. In those experiments in which calcium in creased coronary blood flow the rise in flow was usually maintained or almost so when the infusion was stopped

Calcium had no consistent influence on myocardial oxygen consumption which increased in five experiments and decreased in five. The changes in oxygen consumpt on were not related to changes in coronary blood flow In all experiments, however the tension-time index always decreased in response to calcium. Since stroke work was maintained on the average constant or relatively so, external cardiac efficiency varied w th the changes in oxygen consumption during the infusion of calcium

Influence on myocardial K^+ balance The influence of calcium on myocardial potassium balance was determined during 8 experiments n 4 hearts. In 7 of the 8 experiments, calcium infusion was associated with a net gain of potassium (Table I) Figs. 2 and 3 show the influence of graded infusion of calcium chloride on the myocardial potassium balance of two different

D eject. (msec)		*MVO₂* (ml/m)		*CI* (ml./min)		*TCF* (ml/min)		*TTI* (mm Hg, sec/m)		Net K influx (μEq)
C	*I*	*C*	*I*	*C*	*I*	*C*	*I*	*C*	*I*	
—		8 6	12 6	1 060	980	144	147	—	—	—
160	150	11 4	14 6	1 500	1 100	351	334	1 503	1 098	28
185	160	14 0	13 7	2 900	2 900	270	271	—	—	—
143	143	17 0	14 3	2 300	2 180	332	347	4 617	4 306	0
145	125	17 6	18 8	1 720	1 700	305	404	4 150	2 937	55
143	115	19 2	20 2	1 800	1 800	415	534	4 409	3 164	52
185	165	24 0	22 0	2 620	2 600	456	423	4 749	3 653	140
203	180	19 3	18 9	3 000	2 900	195	23	5 100	3 823	61
213	190	20 8	18 2	3 050	2 950	263	332	4 250	3 570	161
—	—	20 8	19 8	3 080	3 100	309	340	—	—	39
—	—	6 3	7 2	550	600	161	165	—	—	—

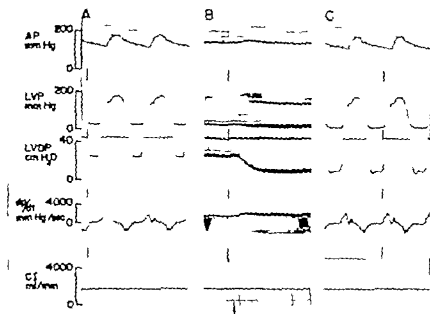


Fig. 1. Influence of CaCl on cardiac performance. AP aortic pressure. LVP left ventricular pressure. LVDP left ventricular diastolic pressure. dp/dt first derivative of left ventricular pressure. CI cardiac output. Heart rate constant throughout at 171. Panel A is control tracing (100 mm per second). Panel B is slow-speed tracing (0.5 mm per second) showing influence of $CaCl_2$ at infusion rate of 50 mg per minute into left coronary artery on the isolated heart. Infusion started at time indicated by vertical arrow. Panel C is fast tracing (100 mm per second) obtained while calcium infusion was continued. Approximately one minute elapsed between tracings. Tracings from Exp. 3c of Table I.

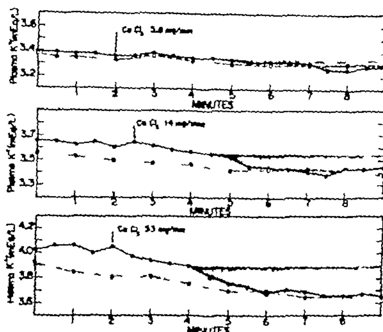


Fig. 2. Influence of graded $CaCl_2$ infusion in the same heart on myocardial K balance. Open circles represent coronary arterial plasma K and closed circles coronary venous plasma K. The shaded area represents the decrease in venous plasma K concentration assumed to be due to the calcium chloride infusion. Data from Exp. 5c, 5a, and 5b of Table I.

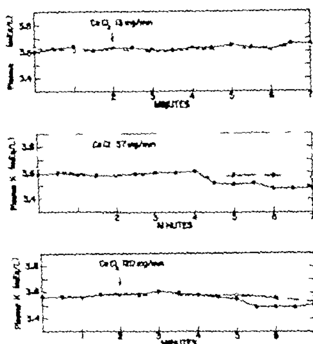


Fig. 3. Influence of graded CaCl infusion in the same heart on myocardial K balance. Legends same as in Fig. 2. Data from Exp. 3b, 3c, and 3d of Table I.

hearts. The shaded area represents the change in venous plasma potassium that is assumed to be due to the infusion of calcium. The time delay between the start of the calcium infusion and the change in venous K^+ concentration is due primarily to the dead space in the sampling system. In the experiment shown in Fig. 2 the extent of the change in potassium balance was, in general, a function of the amount of calcium chloride infused. At an infusion rate of 5.6 mg. per minute the heart gained 39 µEq of K; at 14 mg. per minute, 61 µEq of K; and at 53 mg. per minute, 161 µEq of K for comparable periods of observation. That these changes in K^+ balance represent a net gain of K^+ by the heart rather than the reversal of the loss of K sometimes observed in the control state is indicated by Fig. 3. In this heart, no arteriovenous plasma K difference obtained in the control state. The infusion of 13 mg. per minute of calcium chloride had no discernible influence on myocardial K balance while the infusion of 57 mg. per minute was associated with a gain of 55 µEq of K^+ and the infusion of 170 mg. per minute with a gain of 57 µEq of K^+ for comparable periods of observation. The addition of calcium chloride to whole blood in amounts sufficient to raise the concentration of calcium chloride to 10, 20, and 30 mg. per 100 ml. of whole blood had no influence on plasma K^+ concentration, indicating that the decreases observed in plasma K^+ when calcium chloride is infused into the heart represent a true gain of K^+ by the heart rather than a gain of K^+ by the red cell.

Discussion

The positive inotropic influence of calcium is well known, having been shown to occur in a wide variety of experimental preparations.[1-4] The present experiments confirm these observations and extend them in that the influence of calcium on myocardial performance can occur in the whole heart independent of changes in heart rate, stroke volume, aortic pressure, coronary blood flow, and myocardial oxygen consumption, a finding similar to that obtained for norepinephrine[3] and acetylstrophanthidin. The results of the present experiments are not in accord with those of Feinberg and associates or Sonnenblick and co-workers[11] who found a consistent increase in myocardial oxygen consumption during calcium infusion. The former workers attributed the increase in oxygen consumption during calcium to the greater amount of shortening required to produce the same external work since, under the influence of calcium, heart size is substantially decreased. The latter group attributed the increase in oxygen consumption during calcium to the associated increase in the velocity of myocardial contraction. The extent to which either or both of these factors played a role in the above mentioned or present experiments cannot be determined. Certainly it would be expected that, when aortic pressure, stroke volume, and heart rate are maintained constant, infusion of calcium would decrease the tension developed by the heart as indicated by the decrease in the tension time index,[13] a factor which in itself should decrease myocardial oxygen consumption. Since the tension time index decreased in all the present experiments during calcium infusion while myocardial oxygen consump-

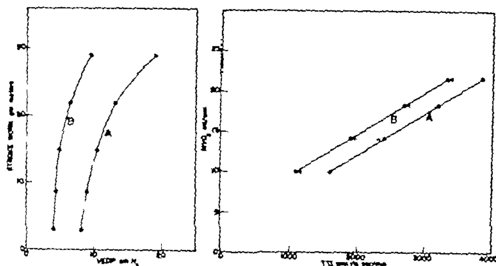


Fig. 4. Diagrammatic representation of the relation between stroke work and left ventricular end-diastolic pressure (left panel) and myocardial oxygen consumption and the tension time index (right panel) before (curve A) and following (curve B) the administration of an inotropic agent. See text for complete description of figure.

tion did not change consistently, the question can be raised as to what factors other than tension influence myocardial oxygen consumption in response to inotropic agents. Such a consideration has been made by Krasnow and associates, who considered the following possibilities: (1) Change in heart size or shape, (2) increase in velocity of ventricular contraction, (3) increased amount of ventricular fiber shortening, and (4) direct metabolic effect of the agent. The extent to which any or all of these factors contributed to the changes observed in the present experiments cannot be ascertained.

Another possibility, however, must be considered. In an earlier communication from this laboratory,[11] it was shown that for any given functional state of the beating heart, the tension time index (TTI) is a major determinant of myocardial oxygen consumption. At the same time, the inotropic effect of calcium as well as norepinephrine[3] and acetyl strophanthidin[4] can obtain independently of a change in MVO_2 and in the presence of a decrease in TTI. That is to say, the relation between TTI and MVO_2 is displaced as is the relation between stroke work and left ventricular end-diastolic pressure. This is shown diagrammatically in Fig. 4. On the left is shown the relation between left ventricular end-diastolic pressure and stroke work before and during the administration of an inotropic agent. The panel on the right shows the change in the relation between TTI and MVO_2 before and during the intervention. A "family" of TTI-MVO_2 curves may thus be described, each curve describing a new functional state of the myocardium. Inotropic agents, therefore, not only change the basic mechanics of cardiac muscle but may also influence the relation between muscle mechanics and oxygen consumption.

The possible relation between tissue movement of calcium and potassium has interested investigators for many years. As early as 1934, it was observed that reduction of the calcium in the medium bathing either nerve[1] or muscle[12] was associated with a loss of potassium from these tissues. Subsequently, it was found that this same relation between calcium and potassium obtained in smooth muscle.[1] The present experiments extend this relationship to the intact heart in that increasing calcium outside the myocardial cell is associated with a net gain of potassium by the heart. The results of these experiments are not consonant, however, with the findings of Kahn and colleagues,[7] who observed that decreasing calcium in the medium bathing isolated guinea pig ven-

tricle decreased K^{42} efflux with no influence on K^{42} influx. Their experiments would suggest that increasing external calcium would decrease myocardial potassium

The present experiments as well as those mentioned above [1-4] indicate that the net movement of calcium is associated with an isodirectional change in potassium balance.

It is well known that calcium norepinephrine, and acetyl strophanthidin increase myocardial contractility The infusion of calcium as shown by the present experiments and the infusion of norepinephrine[3] is associated with an uptake of potassium by the heart while the infusion of acetyl strophanthidin is associated with a loss of myocardial potassium If the assumption that an isodirectional relation obtains between potassium and calcium movements, it is possible that norepinephrine administration is associated with a gain of tissue calcium and acetyl strophanthidin with a loss of tissue calcium At present, however no definitive data are available to confirm or deny this possibility

The results of previous studies,[1-4] indicate that changes in intracellular K^+ can substantially influence myocardial contractility i.e an increase in myocardial potassium of itself decreases contractility while a decrease in intracellular potassium increases myocardial contractility The data presented above for calcium would not appear to support this position. It is not to be assumed however that intracellular potassium is the only factor which can modify cardiac performance. Since intracellular potassium can influence cardiac performance its influence must be taken into account in elucidating the net effect of a given inotropic agent. Thus, it must be considered that the improvement in myocardial performance which occurs under the influence of calcium would be greater if the action of this cation was not associated with an uptake of potassium by the heart

Summary

Studies were performed using the isolated supported heart to determine the myocardial effects of calcium chloride under relatively controlled hemodynamic conditions. The intracoronary infusion of calcium was associated with an increase in myocardial contractility and a net gain of potassium by the heart These changes occurred in the presence of no consistent change in myocardial oxygen consumption It is suggested that changes in myocardial potassium balance may reflect directional changes in myocardial calcium balance

The experiments were carried out with the technical assistance of Mr James Cox, Mr William Anderson, and Mr Samuel Fountain.

REFERENCES

1. Sarnoff S. J Gilmore J P Mitchell, J H., and Remensnyder J P Potassium changes in the heart during homeometric autoregulation and acetyl strophanthidin, Am J Med 34:440, 1963.
2. Sarnoff S J Gilmore, J P Wallace A G., Skinner N S., J Mitchell, J H and Daggett, W M Effect of acetyl strophanthidin therapy on cardiac dynamics, oxygen consumption and efficiency in the isolated heart with and without hypoxia, Am. J Med 37:3, 1964
3. Sarnoff S J Gilmore, J P Weisfeldt, M L., Daggett, W M., and Mansfield, P B Influence of norepinephrine on myocardial oxygen consumption under controlled hemodynamic conditions, Am J Cardiol. 16:217 1965.
4. Sarnoff S J Gilmore, J P and Wallace, A G. Influence of autonomic nerve activity on adaptive mechanisms in the heart, Randall, W C., editor Nervous control of the heart, Baltimore, 1965, The Williams & Wilkins Company p. 54
5. Sarnoff S. J Gilmore, J P McDonald, R. H., J Daggett W M Weisfeldt, M L and Mansfield, P B Relation between myocardial performance O consumption and K balance Am. J Physiol. 211:361 1966.
6. Feinberg, H Boyd, E. and Katz, L. N Calcium effect on performance of the heart, Am J Physiol. 202:643 1962.
7. Hajdu, S. Bioassay for cardiac active principles based on the staircase phenomenon of frog heart, J Pharmacol. & Exper Therap. 120:90, 1957
8. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart J Physiol 4:29 1883
9. Seifen, E., Flacke W and Alper M H Effects of calcium on isolated mammalian heart, Am. J Physiol 207 716, 1964
10. Weidmann, S Effect of increasing the calcium concentration during single heart beat, Experientia 15 128, 1959
11. Sonnenblick, E., Ross, J J Covell, J W Kaiser G. A., and Braunwald, E. Velocity of contraction as determinant of myocardial oxygen consumption Am. J Physiol. 209:917 1965.
12. Sarnoff S. J Braunwald, E., Welch G. H J Case, R B., Stainsby W N and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart with special reference to

the tension-time index, Am. J. Physiol. 192:148, 1958.

13. Krasnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B., and Gorlin, R.: Isoproterenol and cardiac performance, Am. J. Med. 37:514, 1964.

14. Fenn, W. O.: Nerve respiration, Science 79 Suppl. 16, 1934.

15. Fenn, W. O., and Cobb, P. M.: The potassium equilibrium in muscle, J. Gen. Physiol. 17:629, 1934.

16. Tembeck, F., and Strobach, R.: Kaliumabgabe aus glatter muskulatur, Arch. exp. Path. Pharmakol. 228:130, 1956.

Some effects of the hypotensive drug diazoxide on the cardiovascular system

W. G. Nayler, D.Sc.
I. McInnes, F.R.C.S., F.R.A.C.S.
J. B. Swann, M.B.B.S.
D. Race, M.B.B.S.
Valerie Carson, M.Sc.
T. E. Lowe, D.Sc., M.D., F.R.C.P., F.R.A.C.P.
Victoria, Australia

The use of thiazide derivatives in the treatment of hypertension and hypertensive disease is now firmly established. The precise mode of their action is as yet not clear but it is generally thought to be based on their diuretic action. A relatively new thiazide derivative, diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide) is an extremely rapidly acting hypotensive agent which unlike the other thiazide derivatives is devoid of diuretic properties; indeed its prolonged use may cause some retention of sodium and water. Because hypotensive drugs are used so often for the treatment of patients with associated cardiac disease, the effect of such drugs on myocardial performance is of importance. This paper describes an investigation into the effect of diazoxide on cardiac function and, in addition, some investigations into its vasodilator action[1] on the major peripheral vascular beds.

Materials and methods

Anesthesia. Healthy mongrel dogs (15 to 20 kilograms) were premedicated with 30 mg. morphine sulfate (intramuscularly) approximately one hour before anesthesia was induced with sodium thiopentone (20 to 30 mg. per kilograms intravenously). A surgical level of anesthesia was maintained throughout the experiment by giving small supplementary doses of thiopentone from time to time as required. Ventilation was maintained with oxygen from a positive pressure respirator through a cuffed endotracheal tube at a rate of two liters per minute.

Drugs. Dilutions of the following drugs were prepared in 0.9 per cent NaCl solution and added as required directly to the venous circulation in the left ventricular work function studies and to the venous side of the oxygenator in the heart-lung bypass preparations:

5 to 10 mg. per kilogram diazoxide, as *Hyperstat* (Schering Co., New Jersey);
2 μg per kilogram angiotensin as *Hypertensin* (Ciba, Basle);
5 μg per kilogram isoproterenol hydrochloride as *Isuprel* (Winthrop Laboratories, Australia);
5 μg per kilogram norepinephrine bitartrate as *Levophed* (Winthrop Laboratories, Australia);

From the Baker Medical Research Institute, Melbourne, Victoria, Australia.
This investigation was carried out during the tenure of a grant-in-aid from the National Heart Foundation of Australia.
Received for publication March 27, 1963.
Address: Baker Medical Research Institute, Commercial Road, Prahran, S.1, Victoria, Australia.

2 mg. per kilogram atropine sulfate (Hermett David Bull & Co., Australia,
5 mg. per kilogram pentolinium tartrate as Ansolysen (M. & Baker, England)
1 mg. per kilogram propranolol as *Inderal* (Imperial Chemical Industries, England),
2 mg. per kilogram *dl*-4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide hydrochloride as *MJ 1999* (Mead Johnson U. S. A.).

Left ventricular work function curves. Left ventricular work function curves[2] were constructed from a series of experiments before and during the sixty minutes which followed the intravenous administration of diazoxide using a modification of the method originally described by Starling and associates.

Left ventricular "work" function at a particular flow was calculated from the formula

$$W = Q \times (P_A - P_{LA})$$

where W = left ventricular work in gram centimeters per minute, Q = flow in millimeters per minute, P_A = systemic arterial pressure, and P_{LA} = left atrial pressure. The term "work" is used in accordance with its common cardiological usage in the context of Frank-Starling "work" study curves. Strictly speaking, the parameters used are those of power, i.e., work per unit of time.

PREPARATION. The experimental preparation used is shown in Fig. 1. Through a sternal splitting thoracotomy the heart and great vessels were exposed and the pericardium opened. Cannulas were inserted into the superior vena cava (SVC) through the proximal stump of the ligated venous azygos and into the inferior vena cava (IVC) through the right atrial appendage. Tapes were passed around the SVC, IVC, and the pulmonary artery, and an inflow cannula was placed through the wall of the right ventricle and positioned so that its tip lay in the main pulmonary artery distal to the tape. In this way venous return from the great veins was diverted by gravity drainage to a venous reservoir and thence returned by a nonpulsatile pump (Mono Pumps, Australia Pty. Ltd.) into the pulmonary artery. Hence the inflow to the heart and cardiac output could be controlled by adjusting the output of the pump. A cannula was inserted through the wall of the right ventricle to drain the total coronary sinus and Thebesian vein return which was then diverted to a graduated cylinder and then to the venous reservoir. Coronary blood flow was measured by clamping the connection between the graduated cylinder and the reservoir and measuring the time required to collect 100 ml. of blood. The clamp was then released and the blood allowed to return to the venous reservoir.

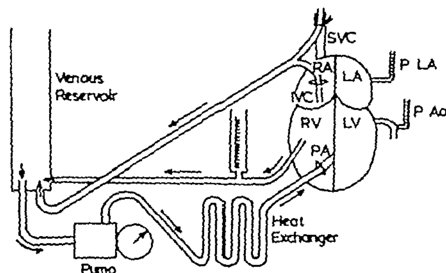


Fig. 1. Schematic diagram of the experimental circuit used for the left ventricular work studies. P LA refers to pressure in left atrium and P Ao to systemic arterial pressure measured in the femoral artery.

Left atrial pressure was measured with a saline manometer connected to a cannula inserted into the left atrium through a branch of the inferior pulmonary vein. Mean systemic pressure was measured with a damped mercury manometer connected to a catheter placed in the left femoral artery.

After all dissection was completed and prior to inserting the cannulas, the dogs were heparinized (2 mg. per kilogram per hour).

Peripheral circulation. Dogs on heart-lung bypass, perfused under conditions of either constant total flow or constant perfusion pressure, were used to investigate the effect of diazoxide on regional blood flow. The method used for the determination of regional blood flow has been described in detail previously.

PREPARATION. Dogs were placed on heart-lung bypass using a Kay-Cross disk oxygenator. The oxygenator was gassed with 100 per cent O and the temperature of the perfusing blood was maintained at 37° C. by means of a stainless steel heat exchanger in the arterial inflow line. Homologous blood and dextrose (3:1) was used to prime the oxygenator. The vascular system was perfused by means of a nonpulsatile (Mono) pump through the right carotid artery. Appropriate cannulation (shown diagramatically in Fig. 2) allowed the independent measurement of outflow from the splanchnic, renal, lower IVC, SVC, and vena azygos vascular fields and coronary sinus. Blood flow through a particular field was measured before and after the addition of diazoxide by clamping the connection between the particular graduated cylinder and the reservoir and measuring the time required to collect 100 ml. of blood. Preliminary experiments showed that pressure in the cannulated venous segments did not change during the collection procedure. Changes in flow due to an opposing pressure head developed during timed collection of blood in the measuring cylinders therefore were considered to be negligible for the purpose of these experiments. Control flow rates were always in excess of 100 ml. per kilogram per minute. Samples of arterial and coronary sinus blood were taken as required to estimate the percentage of hemoglobin O saturation, which was determined spectrophotometrically by a modification of the method of Roos and Rich.

In three heart-lung bypass preparations perfused under conditions of constant perfusion pressure, the effect of diazoxide on the coronary circulation was determined after ventricular fibrillation had been induced by applying ten volts D.C. between two points on the anterior surface of the heart.

Results

Effect of diazoxide on left ventricular work function curves. In a series of control preparations, the output of the pump and inflow to the left atrium was varied from 60 to 160 ml. per kilograms per minute in in

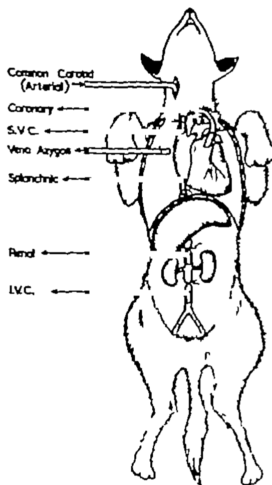


Fig. 2. Schematic diagram showing the cannulation used for measuring blood flow in the various vascular fields.

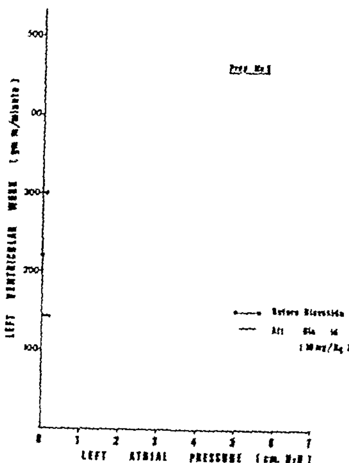


Fig 3 Left ventricular work function curves recorded from a typical preparation before and after the addition of 10 mg per kilogram of diazoxide to the venous circulation. Note that after diazoxide was added the work function curve is displaced to the right, and flattened

crements of approximately 10 ml per kilograms per minute As soon as stable conditions were re-established after each increase in flow mean systemic arterial and mean left atrial pressures were recorded. Calculated left ventricular work was plotted against left atrial pressure for the control series and the resultant curve had a steep slope (Fig 3) indicating that during these control conditions large increments in left ventricular work could be obtained for only small increments in left atrial pressure. Preliminary control studies indicated that these left ventricular work function curves were reproducible for each preparation.

After the addition of 10 mg per kilogram of diazoxide the left ventricular work function curves were consistently displaced to the right and their slope was now less steep compared with those of the control preparations (Fig 3) These changes can be interpreted to mean that diazoxide caused a marked impairment in the capacity of the left ventricle to do work at the control level of left atrial pressure.

A marked increase in coronary blood flow accompanied the diazoxide induced decline in left ventricular work. The results of a typical preparation are shown in Fig 4 and indicate that although left ventricular work was less at all flow rates after the addition of diazoxide than before coronary blood flow was greater

These changes in myocardial function and coronary blood flow were evident two or three minutes after diazoxide was added and persisted for at least 60 minutes.

Effect of diazoxide on the peripheral circulation Preliminary studies indicated that

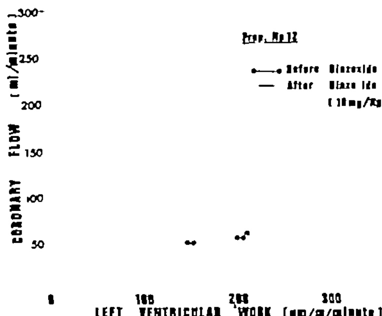


Fig 4 Relationship between left ventricular work and coronary blood flow before and after the addition of 10 mg per kilogram of diazoxide t typical left ventricular work function preparation Left ventricular work and coronary blood flow were estimated simultaneously

blood flow through the various vascular beds in dog heart lung bypass preparations remained constant during three hours of bypass.

CONSTANT TOTAL FLOW CONDITIONS

1 Diazoxide The addition of 10 mg per kilograms diazoxide to dog heart-lung bypass preparations perfused under conditions of constant flow resulted in an immediate and sustained fall in mean systemic pressure and a redistribution of blood throughout the various regional fields of flow The mean results from five preparations are summarized in series A of Table I. These data show that the diazoxide-induced fall in systemic pressure was accompanied by an increase in the proportion of the total blood flow which passed through the coronary, IVC and SVC vascular fields, whereas the percentage of the total blood flow distributed throughout the splanchnic, vena azygos, and renal vascular beds was diminished

To investigate the possibility that this redistribution of blood in the peripheral circulation may have resulted from the geometric changes associated with the marked fall in systemic arterial blood pressure, rather than from the direct action of the drug itself other experiments were performed using smaller concentrations of diazoxide The results of five such preparations which received only 5 mg per kilogram of diazoxide are summarized in series B of Table I Here the mean arterial blood pressure after diazoxide was 65 6 ± 0.5 mm Hg Under these conditions the action of diazoxide was associated with a redistribution of blood in the peripheral circulation similar to that already described

The effect of diazoxide on coronary blood flow was not associated with any marked change in the rate at which the myocardium utilized oxygen, as is shown by the data summarized in Table II

2 Norepinephrine and angiotensin The addition of either norepinephrine or angiotensin to dog heart-lung bypass preparations during the period of hypotension which followed the addition of diazoxide resulted in an immediate pressor response which was not significantly different from that recorded after these same pressor drugs had been added to the control preparations. Thus the addition of 5 μg per kilogram of norepinephrine to control preparations, perfused under conditions of constant flow resulted in an increase of

Table I. Effect of diazoxide on regional distribution of blood in the peripheral circulation of dogs on heart-lung bypass perfused under conditions of constant flow

	Systemic pres. (mm. Hg)	Regional blood flow (ml./Kg./min.)					
		Coronary	Renal	I.V.C.	S.V.C.	Splanchnic	Lungs
Series A. 5 preparations							
Before diazoxide							
Mean	82.5	13.8	18.3	15.9	34.8	53.4	9.1
± S.E.	±1.5	±0.5	±0.2	±0.3	±0.4	±0.6	±0.2
Per cent of flow		(10.7)	(12.4)	(10.8)	(23.6)	(36.3)	(6.2)
After 10 mg./Kg. diazoxide							
Mean	30.0	17.9	11.7	20.5	41.3	47.4	8.4
± S.E.	±0.5	±0.4	±0.1	±0.3	±0.5	±0.5	±0.1
Per cent of flow		(12.2)	(8.0)	(13.9)	(28.0)	(32.0)	(5.7)
Series B. 5 preparations							
Before diazoxide							
Mean	92.0	16.9	15.4	12.3	29.2	46.6	7.7
± S.E.	±1.5	±0.6	±0.3	±0.3	±0.4	±0.6	±0.1
Per cent of flow		(13.2)	(12.0)	(9.6)	(22.8)	(36.4)	(6.0)
After 5 mg./Kg. diazoxide							
Mean	65.5	20.9	10.0	16.3	33.8	40.7	6.4
± S.E.	±1.0	±0.5	±0.5	±0.4	±0.4	±0.6	±0.2
Per cent of flow		(16.4)	(7.8)	(12.6)	(26.4)	(31.8)	(5.0)

Table II. Effect of 10 mg. per kilogram of diazoxide on coronary blood flow and coronary A-V oxygen difference

Preparation No.	Systemic perfusion pressure (mm. Hg)		Coronary flow (ml./Kg./min.)		Coronary A-V O_2 difference (per cent saturation)	
	B	A	B	A	B	A
18	90	61	8.2	9.8	6.2	5.0
19	100	65	7.8	8.8	4.0	3.5
20	110	55	7.3	9.2	9.1	5.8
21	90	65	8.7	9.6	7.1	5.8

B, before, and A, after 10 mg. per kilogram of diazoxide.

75 ± 5 mm. Hg (mean ± S.E. 6 experiments) compared with an increase of 68 ± 6 mm. Hg (mean ± S.E. 6 experiments) when added to these same preparations ten minutes after 10 mg. per kilogram of diazoxide had been added. Similarly, 2 μg per kilogram of angiotensin caused an increase of 52 ± 4 mm. Hg (mean ± S.E. 5 experiments) before and 55 ± 5 mm. Hg (mean ± S.E. 5 experiments) when added after the prior addition of 10 mg. per kilogram of diazoxide.

3. Propranolol and MJ 1999. The prior administration of either propranolol or MJ 1999, both of which are β-adrenergic receptor antagonists, failed to modify the hypotensive action of diazoxide or its effect on the regional distribution of blood

Table III Effect of 10 mg per kilogram of diazoxide on regional distribution of blood in the peripheral circulation of five β-blocked dog heart-lung bypass preparations perfused under conditions of constant flow

	Systemic pressure (mm Hg)	Regional blood flow as per cent of total flow					
		Coronary	Renal	IVC	SVC	Splanchnic	Azygos
Propranolol (1 mg /Kg)							
*Series 3 preparations**							
Before diazoxide							
Mean	92 0	7 2	12 1	14 8	28 4	30 7	6 8
± S.E.	±2 0	±0 5	±0 8	±0 6	±1 0	±0 8	±0 2
After 10 mg /kg diazoxide							
Mean	39 2	9 6	8 2	18 2	31 2	26 3	5 4
± SE	±0 8	±0 4	±0 3	±1 1	±1 2	±1 1	±0 3
MJ 1999 (2 mg /Kg)							
Series 2 preparations							
Before diazoxide							
Mean	85 2	8 8	12 3	14 2	27 6	30 8	6 3
± SE	±0 6	±0 5	±0 6	±0 5	±0 8	±1 1	±0 4
After 10 mg /kg diazoxide							
Mean	36 4	10 1	8 6	18 6	32 0	24 8	5 9
± S E.	±1 0	±0 3	±0 4	±0 8	±0 5	±1 0	±0 2

*In each preparation effectiveness of β-blockade was checked with isoproterenol (2 μg per kilogram intravenously)

in the peripheral circulation The mean results recorded following the addition of diazoxide to five β-blocked preparations are summarized in Table III In three of these preparations β-adrenergic blockade was effected with propranolol and in the other two preparations with MJ 1999 The effectiveness of β-blockade was established for each preparation by the failure of 2 μg per kilogram of isoproterenol to lower systemic pressure or to cause any change in coronary blood flow

4 Atropine and pentolinium The effect of diazoxide on the peripheral circulation was not modified by the prior addition of either 2 mg per kilogram of atropine or 5 mg per kilogram of pentolinium tartrate

CONSTANT PERFUSION PRESSURE CONDITIONS

1 Diazoxide The addition of 10 mg per kilograms of diazoxide to dog heart-lung bypass preparations perfused under conditions of constant pressure produced a marked change in the regional distribution of the blood The mean results from these experiments are summarized in Table IV

In series A the perfusion pressure was maintained at 40 mm. Hg throughout the experiments while in series B a higher perfusion pressure, 70 mm Hg, was maintained. In both series of experiments diazoxide caused a reduction in the resistance to blood flow in all the vascular beds studied. The coronary SVC and IVC regional fields now received a greater proportion of the total blood flow while the renal and azygos beds received a smaller proportion

The effect of diazoxide on the resistance to blood flow in the peripheral circulation was not blocked by the prior administration of atropine (5 experiments) pentolinium (5 experiments) or of the β-adrenergic antagonists, MJ 1999 (4 experiments) or propranolol (4 experiments)

2 Ventricular fibrillation Diazoxide reduced the resistance to blood flow in the coronary circulation of those preparations in which the ventricles were fibrillating The dilator effect of diazoxide on the coronary circulation therefore, cannot be due simply to the diazoxide induced decline

Table IV. Effect of 10 mg. per kilogram of diazoxide on regional distribution of blood in the peripheral circulation of dog heart-lung bypass preparations perfused under conditions of constant systemic pressure

	Systemic pressure (mm. Hg)	Regional blood flow (ml./Kg./min.)					
		Coronary	Renal	IVC	SVC	Splanchnic	Azygos
Series A: 6 preparations							
Before diazoxide							
Mean	40.0	7.9	7.1	7.2	11.8	15.7	7.6
± S.E.		±0.2	±0.2	±0.3	±0.3	±0.4	±0.2
Per cent of flow		(13.8)	(12.3)	(12.5)	(20.6)	(27.6)	(13.2)
After 10 mg./Kg. of diazoxide							
Mean	40.0	18.2	13.8	17.6	30.4	29.6	12.6
± S.E.		±0.3	±0.2	±0.2	±0.4	±0.5	±0.3
Per cent of flow		(14.9)	(11.2)	(14.4)	(24.8)	(24.2)	(10.5)
Series B: 6 preparations							
Before diazoxide							
Mean	70.0	14.3	17.5	14.6	17.5	34.2	9.8
± S.E.		±0.3	±0.2	±0.3	±0.3	±0.5	±0.2
Per cent of flow		(13.3)	(16.2)	(13.5)	(16.2)	(31.7)	(9.1)
After 10 mg./Kg. of diazoxide							
Mean	70.0	26.6	22.8	26.4	28.6	48.0	10.8
± S.E.		±0.4	±0.2	±0.2	±0.4	±0.5	±0.2
Per cent of flow		(15.9)	(13.7)	(15.8)	(17.1)	(28.7)	(6.5)

in the external work done by the myocardium. The diazoxide-induced increase in coronary blood flow was not associated with any marked change in myocardial oxygen consumption, as is shown by the data listed in Table II.

Discussion

The concept and validity of myocardial function curves has been well documented by Sarnoff and Berglund. They demonstrated that in any given circulatory state there is a consistent relationship between atrial pressure and ventricular stroke work, and that this relationship is reflected in the ventricular work function curves. Sarnoff and Berglund found that in any particular animal a series of similar work function curves could be generated by altering those parameters which influence myocardial performance. Increasing the level of circulatory catecholamines[3] and sympathetic nerve stimulation produced a shift of the work function curves for a particular animal to the left, indicating that the capacity for doing external work at the same atrial pressure and hence at the same left ventricular diastolic fiber length was enhanced. Other studies have shown that agents such as heat,[10] anoxia, ventricular distension,[11] and halothane[5] displaced the ventricular function curves to the right. This shift to the right can be interpreted to mean that the capacity of the left ventricle for doing external work at the same atrial pressure and hence at the same left ventricular end-diastolic fiber length[12] is diminished.

The results reported in the present study indicate that diazoxide displaces the left ventricular function curves to the right so that myocardial function at a particular atrial pressure is reduced by this drug. These results are supported by data published by Rubin and associates, which shows that a small rise in right atrial pressure is associated with the action of diazoxide. Rubin regarded this as a non-

significant increase in right atrial pressure but the ventricular function curve studies of Sarnoff and Burglund[3] have shown that such a rise in right atrial pressure can produce greater changes in right ventricular performances than does a similar rise in left atrial pressure on left ventricular performances.

In the present study the effect of diazoxide on myocardial performance has been investigated over a dynamic range of myocardial work capacity[4] rather than at one particular level of work output. Such an approach would seem to be necessary if the real effect of drugs on myocardial performance is to be gauged.

Diazoxide caused a marked reduction in the resistance to blood flow in the peripheral circulation including the regional fields in the coronary, IVC, and SVC circulations. This dilator effect of diazoxide cannot be accounted for in terms of an altered α or β adrenergic function, since the response was not blocked by β-adrenergic blockade[7,8] nor did diazoxide interfere with the constrictor effect of norepinephrine on the peripheral vasculature. The dilator effect of diazoxide on the coronary circulation apparently is not associated with any marked change in myocardial oxygen consumption, the amount of oxygen used per milliliter of coronary blood flow being approximately the same before and after the addition of diazoxide. This dilator effect of diazoxide on the coronary circulation occurred in fibrillating hearts as well as in hearts which were performing useful mechanical work so that it probably is not due simply to the depressant effect of diazoxide on the myocardium.

The action of diazoxide on the peripheral circulation was not modified by ganglionic blockade nor did it interfere with the pressor effect of angiotensin.

Recently the use of hypotensive drugs in the treatment of shock and during surgery has attracted attention[10]. The use of the α adrenergic antagonist dibenzylene[11] has been advocated because it restores blood flow in the peripheral circulation by antagonizing the α adrenergic constrictor receptors[1] in the peripheral circulation. While doubt must exist in applying the results described in the present paper to situations and species other than dogs on heart lung bypass, the results indicate that drugs which decrease peripheral vascular resistance by a direct effect on smooth muscle may similarly depress myocardial contractility.

Summary

The action of diazoxide (7-chloro-3-methyl 1,2,4 benzothiadiazine), a nondiuretic thiazide derivative, on the peripheral circulation and on left ventricular function was investigated. This drug was found to cause a marked reduction in the resistance to blood flow in the peripheral vasculature, so that the percentage of the total blood distribution to the coronary, IVC, and SVC circulations increased while the percentage of the total blood flow distributed to the azygos, renal, and splanchnic circulations decreased. The dilator effect of diazoxide on the coronary circulation was not associated with any change in myocardial oxygen consumption. Diazoxide displaced left ventricular function curves to the right, indicating a diminution in the capacity of the left ventricle for doing external work.

The diazoxide used in these investigations was generously donated by the Schering Corporation, U. S. A., and propranolol by Imperial Chemical Industries of England.

REFERENCES

1. Rubin, A. A., Roth, F. E., Taylor, R. M., and Rosenkilde, H.: Pharmacology of diazoxide, an antihypertensive, non-diuretic benzothiadiazine, J. Pharmacol. & Exper. Therap. 136:344, 1962.
2. Rubin, A. A., Zitowitz, L., and Hausler, L.: Acute circulatory effects of diazoxide and sodium nitrate, J. Pharmacol. & Exper. Therap. 140:46, 1963.
3. Sarnoff, S. F., and Berglund, E.: Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation 9:706, 1954.
4. Stirling, G. R., Morris, K. N., and Race, D.: The effect of induced asystole on ventricular function, Australia & New Zealand J. Surg. 31:81, 1961.
5. Nayler, W. G., Race, D., Price, J. M., and Lowe, T. E.: Some effects of a cardioactive fraction isolated from human blood plasma on the peripheral circulation, Circulation Res. 18:1, 1966.
6. Ross, A., and Rich, J. A.: Spectrophotometric determination of oxyhaemoglobin saturation

and oxygen content of blood, J. Lab. & Clin. Med. 40:431, 1952.

7. Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H., and Dornhorst, A. C.: A new adrenergic beta-receptor antagonist, Lancet 1:1080, 1964.

8. Lish, P. M., Weikel, J. H., and Dungan, H. W.: Pharmacological and toxicological properties of two new β-adrenergic antagonists, J. Pharmacol. Exper. & Therap. 149:161, 1965.

9. Mitchell, J. H., Linden, R. J., and Sarnoff, S. J.: Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length, Circulation Res. 8:1100, 1960.

10. Merriam, T. W., Jr.: Myocardial function following thermal injury, Circulation Res. 2:669, 1962.

11. Race, D., Stirling, G. R., and Morris, K. N.: Induced ventricular fibrillation in open heart surgery, J. Thoracic & Cardiovas. Surg. 47:271, 1964.

12. Stirling, G. R., Morris, K. N., Orton, R. H., Boake, W. C., Race, D., Kinross, F., Thomson, J. W., and Crosby, W.: Halothane and circulatory occlusion: some experimental and clinical observations, Brit. J. Anaesth. 33:262, 1960.

13. Case, R. M., Berglund, E., and Sarnoff, S. J.: Ventricular function: quantitative relationship between coronary flow and ventricular function with observations on unilateral failure, Circulation Res. 2:319, 1954.

14. Ahlquist, R. P.: A study of the adrenotropic receptors, Am. J. Physiol. 153:586, 1948.

15. Arbulu, A., and Thal, A. P.: The hemodynamic effects of alpha and beta adrenergic blockade, Surgery 60:60, 1966.

16. Lillehei, R. C., Longerbeam, J. K., Bloch, J. H., and Manax, W. W.: The nature of irreversible shock: experimental and clinical observations, Ann. Surg. 160:682, 1964.

17. Thal, A. P., and Wilson, R. F.: Shock, in Current problems in surgery, Chicago, 1965, Year Book Medical Publishers, Inc., p. 43.

Cardiovascular adrenergic activity of dopamine in the dog

William L. Black, M.D.
Ellis L. Rolett, M.D.
Chapel Hill, N. C.

Catecholamines influence cardiovascular function through both α- and β-adrenergic receptor stimulation. Dopamine (3,4-dihydroxyphenylethylamine), the intermediate biological precursor of norepinephrine, demonstrates both vasopressor and inotropic activity in the dog when administered as a single injection in doses greater than 10 μg per kilogram. On the contrary, smaller amounts of dopamine do not produce pressure elevation. The latter response suggests that low doses of dopamine manifest little if any α-adrenergic activity in the intact dog. Nevertheless, the cardiovascular action of continuous low-dose infusions of dopamine is significantly different from that of isoproterenol, a synthetic catecholamine which exerts a pure β-adrenergic effect. In addition to an inotropic effect, isoproterenol administration leads to a lower blood pressure, a fall in left ventricular end-diastolic pressure and volume, and tachycardia. As shown in previous work from this laboratory, dopamine infused at rates between 1 and 10 μg per kilogram per minute shares a potent inotropic effect with isoproterenol in the intact dog but, in contrast, fails to alter mean aortic pressure, left ventricular end-diastolic pressure and volume, and heart rate.

The following study was performed to detect whether dopamine exerts any α-adrenergic action at constant infusion rates of 10 μg per kilogram per minute or less. Such an action on the part of dopamine, although overshadowed by its inotropic activity, would serve to explain at least partially the differences in response to dopamine and isoproterenol. In this study the action of dopamine was examined during β-adrenergic blockade, and it was thereby confirmed that low doses of dopamine do possess vasoconstrictor properties. At the same time, observations on the performance of the β-blocked left ventricle were possible.

Materials and methods

Procedure. A total of 15 intact mongrel dogs weighing between 15 and 30 kilograms were anesthetized with 50 to 70 ml. of chloralose (1.6 per cent) and urethan (16 per cent) 20 minutes after the intramuscular injection of morphine sulfate (3 mg. per kilogram). A relatively steady state of anesthesia was maintained by 5 to 10 ml. supplements of the chloralose-urethan

From the Department of Medicine, University of North Carolina and North Carolina Memorial Hospital, Chapel Hill, N. C.

Supported by National Heart Institute Grants HE 08188 and 5 T1 HE 5486, and by a grant from the North Carolina Heart Association.

Presented before the Thirty-eighth Scientific Sessions of the American Heart Association in Bal Harbor, Fla., October 1965.

Received for publication April 3, 1967.

solution approximately every 90 minutes. Ventilation was controlled with a Harvard pump through a cuffed endotracheal tube.

The experimental model has been previously described in detail. The left ventricle and ascending aorta were catheterized with 50 cm. 7F Dacron catheters introduced through the left carotid and one femoral artery. Pressures were measured with Statham P23Db transducers. Peak velocity of left ventricular pressure rise (dp/dt) was derived by electronic differentiation of the left ventricular pressure signal. The frequency response of the catheter systems and differentiating circuit was linear (± 5 per cent) to at least 75 cycles per second. Left ventricular end-diastolic pressure was evaluated from high-gain left ventricular tracings. Cardiac output was determined in duplicate by indicator dilution (indocyanine green) and ventricular volume by thermodilution.[7] Lead 2 of the electrocardiogram (ECG) was constantly monitored. All signals were recorded on a Sanborn 550M photographic recorder.

Approximately one hour after the induction of anesthesia, β-adrenergic receptor blockade was achieved by intravenous administration of propranolol (0.4 mg. per kilogram) and maintained with 0.2 mg. per kilogram every 45 minutes.[8] Base-line observations were made 30 minutes after the initial propranolol dose. Ten dogs (Group I) were then given intravenous infusions of dopamine diluted in isotonic saline at rates of 5, 8, and 10 μg per kilogram per minute for 30 minutes. During the maximum dopamine infusion rate nine of these dogs were given intravenous phenoxybenzamine (3 mg. per kilogram) to block α-adrenergic receptors. Five additional dogs (Group II) served as controls and were given equal volume infusions of isotonic saline alone for corresponding 30 minute intervals. All observations were repeated during the last five minutes of each infusion period and within 15 minutes after phenoxybenzamine administration.

Calculations. For each period of observation average values for heart rate, stroke volume (SV), systolic ejection period (SEP), and systolic ejection rate (SER = SV/SEP) were calculated (see Table I). Mean aortic ejection pressure (EP) was obtained by planimetry of the aortic pressure tracing over a full respiratory cycle. Mean ejection resistance (ER) was derived from the equation ER = EP/SER.[9] Mean left ventricular end-diastolic volume (EDV) was computed from six to eight thermodilution curves during each observation period. Mean left ventricular end-systolic volume (ESV) was obtained from the relation ESV = EDV − SV. The left ventricle was assumed to be spherical in shape and its mean circumferential shortening distance (CSD) was calculated from CSD = $2\pi(r_1 - r_2)$ where r_1 and r_2 are the respective left ventricular end-diastolic and end-systolic radii.

Analysis of data. Observations at each dopamine dose level during saline infusions or following phenoxybenzamine were compared with appropriate base-line values. Paired t testing was used to evaluate the significance of mean differences between experimental and base line observations within each group of animals. Unpaired t testing was used in evaluating the mean differences in observations between Groups I and II. Standard errors of individual mean differences were calculated from standard formulas of statistical analysis.

Table I. Mean (± SE) values of base-line observations in dogs pretreated with propranolol

	Group I*	Group II†
Heart rate (beats/min.)	84 ± 7	79 ± 6
Stroke volume (ml.)	28 ± 3	30 ± 3
Peak dp/dt (mm. Hg/sec.)	2,456 ± 175	3,033 ± 282
Systolic ejection rate (ml./sec.)	127 ± 12	141 ± 13
Mean ejection pressure (mm. Hg)	120 ± 6	124 ± 4
Mean ejection resistance (mm. Hg/ml./sec.)	1.00 ± 0.10	0.92 ± 0.09
Circumferential shortening distance (cm.)	1.9 ± 0.1	2.0 ± 0.2

*Animals treated subsequently with dopamine and phenoxybenzamine.
†Animals which served as saline treated control group.

3-Hydroxytyramine HCl, California Corporation for Biochemical Research.

Results

The base-line values obtained after the institution of β-adrenergic blockade are listed in Table I. The subsequent observations, made during dopamine and saline infusion follow.

Fig. 1 illustrates the changes in stroke volume and heart rate during dopamine infusion and for the saline-treated control group. Increasing doses of dopamine produced a progressive fall in stroke volume, and at each dose level this change was significant with respect to both the base-line value ($p < 0.01$) and the saline-treated group ($p < 0.05$). At the 10 µg per kilogram per minute level stroke volume had fallen 23 per cent from its initial value. Phenoxybenzamine returned the stroke volume to a level which was not significantly different from the base-line value. Although the heart rate for both groups fell slightly, the change was not significant in either group.

In neither group during treatment did a significant change take place in left ventricular end-diastolic pressure or mean aortic ejection pressure. The dopamine-treated dogs, however, did show a significant fall (19 mm. Hg; $p < 0.01$) in ejection pressure after the administration of phenoxybenzamine.

Two velocity functions of left ventricular performance are illustrated in Fig. 2. Peak dp/dt noted to occur during the isovolumic phase of ventricular contraction did not change with respect to base-line values either during dopamine administration or during saline infusion. Dopamine infusion, in contrast to saline infusion, produced a progressive and significant ($p < 0.05$) decline in the mean rate of systolic ejection. This was a decline of 25 per cent from the control value at the highest dopamine dose. This variable returned to its base-line level following intravenous phenoxybenzamine.

Circumferential shortening distance, an index of myocardial fiber shortening, progressively declined at the same time as the calculated systolic resistance to left ventricular ejection rose in the dopamine-treated animals (Fig. 3). At 10 µg per kilo-

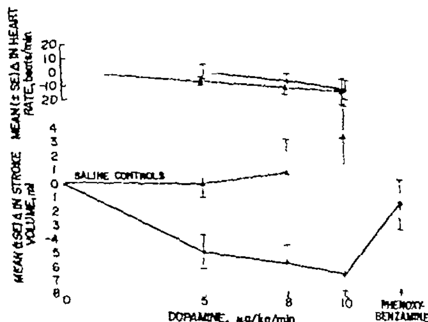


Fig. 1. Mean (± S.E.) differences in heart rate and stroke volume for both groups of dogs. The saline-treated controls (dashed lines) were comparable to the dopamine-treated group (solid lines) with respect to the amount of saline given and time elapsed from the start of each infusion level. Both groups had been pretreated with propranolol. No significant change in heart rate occurred, whereas a progressive fall in stroke volume was noted in the dopamine-treated dogs.

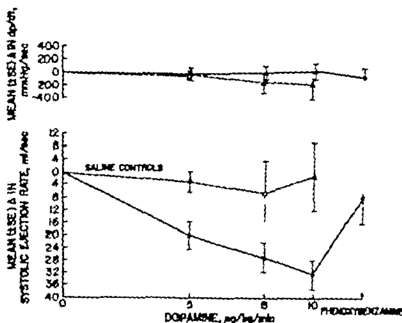


Fig. 2. Mean (± S.E.) differences in peak dp/dt and systolic ejection rate. Peak dp/dt remained unchanged despite dopamine or saline treatment. During the ejection period however systolic ejection rate declined significantly in the dopamine-treated animals and returned to control levels following phenoxybenzamine infusion.

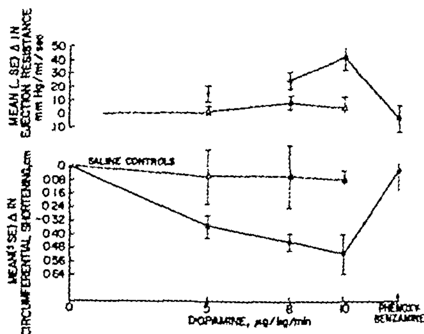


Fig. 3. Mean (± S.E.) differences in circumferential shortening distance and ejection resistance. The dopamine-treated group showed a significant ($p < 0.01$) decline in circumferential shortening and a corresponding increase in mean ejection resistance. No significant change in either variable was encountered in the saline-treated group.

gram per minute this represented a 26 per cent fall in circumferential shortening and a 43 per cent increase in ejection resistance. Neither variable was changed significantly during saline infusion. Phenoxybenzamine again countered the action of dopamine.

Discussion

Previous studies of the cardiovascular responses to systemically administered dopamine have emphasized either augmented myocardial contractility or mesenteric and renal vasodilatation in the dog and man.[11] Few investigations have examined the α-adrenergic or vasoconstrictor activity of dopamine in the intact animal. In the perfused canine extremity, however, intra-arterial injection of dopamine (0.1 to 128 μg) has caused vasoconstriction.[1] Moreover, Allwood and Ginsburg[12] have presented evidence that intra-arterial dopamine infusion (50 μg per minute) will produce vasoconstriction in the human forearm and hand and that phenoxybenzamine prevents this response. Nevertheless, previous studies of the net effect of systemically administered dopamine have failed to show any evidence of vasoconstriction at doses of 10 μg per kilogram or below. In fact, these same studies have demonstrated a fall in total peripheral vascular resistance consistent with a net vasodilatory effect.[12]

The results of the present study proved interesting, therefore, because dopamine infusions of 5, 8, and 10 μg per kilogram per minute during β-adrenergic receptor blockade produced a progressive increase in systolic ejection resistance. Phenoxybenzamine, an α-adrenergic receptor blocking agent, reversed this action of dopamine. Therefore, the ability of dopamine to increase arterial resistance—a property which became evident at low doses only during β-adrenergic blockade—appears to be mediated through α-adrenergic stimulation.

A comparison of the actions of dopamine in this dose range with those of isoproterenol and norepinephrine permits a conclusion concerning the relative strength of the α- and β-stimulating properties of these agents. In the adrenergically intact animal isoproterenol causes a decline in mean aortic pressure at the same time that ventricular ejection is augmented.[4] No vasoconstrictor activity has been demonstrated for isoproterenol in other studies. On the other hand, norepinephrine administered intravenously appears to exert a predominant vasoconstrictor effect, manifest by an increase in arterial pressure and depressed ventricular ejection. Norepinephrine also stimulates β receptors since β-adrenergic blockade intensifies the depression of ventricular ejection by this catecholamine.[13] Consequently, dopamine appears to possess properties intermediate to those of isoproterenol and norepinephrine, namely α-adrenergic activity which is overshadowed by a β-stimulating action. This combined α- and β-adrenergic activity probably accounts for the constant aortic pressure during dopamine infusion in dogs not pretreated with propranolol.[4]

In the current study, a vasoconstrictor action for dopamine was inferred from the calculated increase in resistance to left ventricular outflow. Ejection resistance has been defined as the ratio of mean ejection pressure to mean systolic ejection rate and an equivalent expression is the ratio of the systolic area under the aortic pressure curve to stroke volume. Several of the possible alterations in the relationship between left ventricular ejection pressure and systolic ejection rate which may be induced by vasoactive drugs are represented in Fig. 4. A decrease in ejection resistance can be indicated diagrammatically by the arrow from point *A* to *B*. Isoproterenol or low doses of dopamine in the adrenergically intact dog can effect this type of change. On the other hand, an increase in ejection resistance by implication may be associated with either an increase in ejection pressure, or a decline in ejection rate, or with both effects. The response of the isolated heart to a mechanical increase in outflow resistance has been found to be one of increased aortic pressure but unchanged stroke volume, equivalent to a shift from point *A* to *C* in Fig. 4. Systemically administered norepinephrine in the human subject exhibits a similar action. In contrast, the response to the pharmacological increase in ejection resistance in the present study is represented by the arrows joining points *A* and *D* and characterized by a relatively unchanging

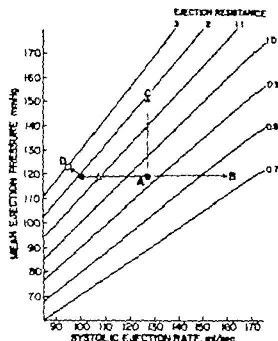


Fig. 4. Interrelationships among mean ejection pressure, systolic ejection rate, and calculated ejection resistance. Theoretically, altered ejection resistance can be reflected in changes in mean ejection pressure (for example, shift from *A* to *C*) or systolic ejection rate (shift from *A* to *B*). The response to dopamine in propranolol pretreated animals is shown by the shift from point *A* to *D* (3 μg./kg./min = △; 8 μg./kg./min = ●; 10 μg./kg./min = ○): an increased ejection resistance which is manifest chiefly as a fall in systolic ejection rate.

ejection pressure in the face of a declining systolic ejection rate and stroke volume. An explanation of this difference in response can only be conjectural. A likely explanation, however, lies in the consequence of β-adrenergic blockade. The present findings suggest that under the conditions of propranolol induced β-adrenergic blockade the left ventricle of anesthetized dogs is unable to maintain the previous degree of muscle shortening and therefore stroke volume when exposed to an augmented outflow resistance. A decrease in muscle shortening under these conditions does not necessarily mean a reduction in myocardial contractility. The peak velocity of left ventricular pressure rise is influenced by heart rate, aortic blood pressure, ventricular end-diastolic pressure, and myocardial contractility.[11] In the present study heart rate, aortic, and end-diastolic pressures were essentially constant. Accordingly, it appears that during the isovolumic phase myocardial contractility, as represented by an unchanged dp/dt, was unaffected by the increased outflow resistance.

Summary

In previous studies, dopamine infused at low doses in intact dogs has exerted an inotropic effect without change in systemic blood pressure. This was in contrast to the action of isoproterenol, a pure β-adrenergic agent with which a lowering of mean blood pressure usually accompanies the inotropic effect. This difference suggested that even at lower doses dopamine possessed α-adrenergic properties which were undetectable as a pressor response. The present study was conducted to demonstrate such α activity and to evaluate its effects upon left ventricular performance following β-adrenergic blockade. The results confirm that dopamine in low infusion doses does possess α-adrenergic activity. Such activity was essentially masked during dopamine infusion alone but was uncovered in the presence of β-adrenergic blockade. Possibly of greater significance, these data indicate that the intact canine left ventricle, while preserving a relatively steady state of isovolumic contractility, may be unable to maintain stroke volume in the face of increased ejection resistance during propranolol induced β-adrenergic blockade.

Propranolol (Inderal) was kindly supplied by Dr. Alex Edwards, Ayerst Laboratories.

REFERENCES

1. Furchgott, R. F.: Receptors for sympathomimetic amines, *in* Vane, J. R., Wolstenholme, G. E. W., and O'Connor, M., editors: Adrenergic mechanisms, Boston, 1960, Little, Brown & Co., pp. 246-252.
2. Ahlquist, R. P.: A study of the adrenotropic receptors, Am. J. Physiol. 153:586, 1948.
3. McDonald, R. H., Jr., and Goldberg, L. I.: Analysis of the cardiovascular effects of dopamine in the dog, J. Pharmacol. & Exper. Therap. 140:60, 1963.
4. Eble, J. N.: A proposed mechanism for the depressor effect of dopamine in the anesthetized dog, J. Pharmacol. & Exper. Therap. 145:64, 1964.
5. Krasnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B., Jr., and Gorlin, R.: Isoproterenol and cardiovascular performance, Am. J. Med. 37:514, 1964.
6. Black, W. L., and Rolett, E. L.: Dopamine-

induced alterations in left ventricular performance, Circulation Res. 19:71, 1966.

7. Rolett, E. L., Sherman, H., and Gorlin, R.: Measurement of ventricular volume by thermodilution: an appraisal of technical errors, J. Appl. Physiol. 19:1164, 1964.

8. McInerny, T. K., Gilmour, D. P., and Blinks, J. R.: Comparison of effects of propranolol and other cardiac adrenergic blocking agents on inotropic and chronotropic actions of catecholamines, Fed. Proc. 24:712, 1965.

9. Wilcken, D. E. L., Charlier, A. A., Hoffman, J. I. E., and Guz, A.: Effects of alterations in aortic impedance on the performance of the ventricles, Circulation Res. 14:283, 1964.

10. McNay, J. L., McDonald, R. H., Jr., and Goldberg, L. I.: Direct renal vasodilatation produced by dopamine in the dog, Circulation Res. 16:510, 1965.

11. McDonald, R. H., Jr., Goldberg, L. I., McNay, J. L., and Tuttle, E. P., Jr.: Effects of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow, J. Clin. Invest. 43:1116, 1964.

12. Allwood, M. J., and Ginsburg, J.: Peripheral, vascular and other effects of dopamine infusions in man, Clinical Sc. 27:271, 1964.

13. Horwitz, D., Fox, S. M., III, and Goldberg, L. I.: Effects of dopamine in man, Circulation Res. 10:237, 1962.

14. Ginsburg, J., and Cobbold, A. F.: Effects of adrenaline, noradrenaline, and isopropylnoradrenaline in man, *in* Vane, J. R., Wolstenholme, G. E. W., and O'Connor, M., editors: Adrenergic mechanisms, Boston, 1960, Little, Brown & Company, pp. 173-189.

15. Harris, W. S., Schoenfeld, C. D., Brooks, R. H., and Weissler, A. M.: Demonstration of a beta component in the hemodynamic actions of norepinephrine in man, Clin. Res. 13:209, 1965.

16. Sarnoff, S. J., Mitchell, J. H., Gilmore, J. P., and Remensnyder, J. P.: Homeometric autoregulation in the heart, Circulation Res. 8:1077, 1960.

17. Ribeiro, J., Wendt, V. E., Ramos, H., Gudbjarnason, S., Bruce, T. A., and Bing, R. J.: The effects of norepinephrine on the hemodynamics and myocardial metabolism of normal human subjects, Am. Heart J. 68:672, 1964.

18. Wallace, A. G., Skinner, N. S., Jr., and Mitchell, J. H.: Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Am. J. Physiol. 205:30, 1963.

Case reports

The occurrence of primary pulmonary hypertension in twins with a review of etiological considerations

Stephen W. Czarnecki, Lieutenant Colonel, MC, USA
*Harvey M. Rosenbaum, M.D.***
*Herbert L. Wachtel, Major, MC, USA****
New York, N. Y.

Primary pulmonary hypertension has been defined as a disease of unknown etiology. The increased pulmonary vascular resistance occurs in the absence of any recognizable lesion in the heart or in the pulmonary parenchyma. The advent of cardiac catheterization procedures has allowed physiologists and cardiologists a means of directly measuring the pulmonary artery pressure. This capability, in turn, has revealed the fact that primary pulmonary hypertension is far from being a rare disease.[1]

A review of published series on primary pulmonary hypertension reveals the fact that many familial cases have been reported.[1] Indeed, this fact may have some bearing on the etiology. In a hope to shed further light on this aspect, we are reporting what we believe to be the first two cases reported in twins. Both sisters have died and thus we have necropsy confirmation of the diagnosis.

Case reports

Twin B. R. The patient was a 24-year-old Caucasian woman. She was admitted to the hospital in premature labor with vaginal bleeding at 1:30 A.M. on October 9, 1960. Her expected date of confinement was December 14, 1960. Except for some shortness of breath, her prenatal course had been uneventful. On admission to the hospital, she was found to have clinical evidence of an increase in her pulmonary vascular resistance. Specifically, she had a right ventricular heave with increased intensity of the pulmonic component of the second sound. The electrocardiogram (ECG) (Fig. 1) confirmed the right ventricular hypertrophy.

During labor, bleeding was minimal and at 2:40 A.M. the patient was taken to the delivery room where she was given a pudendal block. An amniotomy was performed and spontaneous delivery of a premature female infant occurred at 2:59 A.M.

Shortly thereafter, the patient complained of shortness of breath and was given oxygen by mask and 15 mg. of morphine sulfate intramuscularly. At this time her lungs were clear. Her respirations became more labored and the patient became cyanotic and nonresponsive. An endotracheal tube was passed and her respirations were maintained mechanically. Within minutes, she had no pulse and no heart sounds. The chest was opened and cardiac massage instituted. In spite of all efforts there was no return of cardiac activity. The patient was pronounced dead at 4:00 A.M. on October 9, 1960.

Pathologic report. At autopsy, the heart was found to be enlarged due to a hypertrophied right ventricle. The most striking histologic abnormalities were limited to the pulmonary vascular system.

This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

Received for publication April [illegible] 1962.

*Formerly Chief of Cardiovascular Service, Letterman General Hospital, San Francisco, Calif. Present address: Chief, Department of Medicine, U. S. Army Hospital, Heidelberg, APO New York, N. Y. 09102.
**Resident in Medicine, Cleveland Clinic, Cleveland, Ohio.
***Chief, Cardiovascular Service, Beaumont General Hospital, El Paso, Texas.

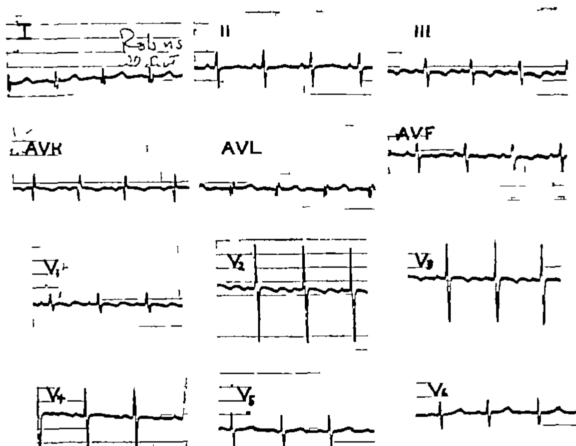


Fig. 1. ECG (Twin B. R.) showing right ventricular hypertrophy.

Most of the smaller arteries and the arterioles showed some degree of intimal proliferation, subintimal thickening, and fibrosis with medial hypertrophy. In many of the vessels, only pinpoint lumina remained and the intimal proliferation in many areas was of such striking degree that numerous irregular clefts, slits, and plexiform configurations were formed. In some degree these changes were suggestive of recanalization of thrombi but evidence of thrombus or embolism, as such, was not apparent. The larger vessels showed some hypertrophy of the muscle layers and minimal patchy subintimal thickening.

Twin B. A 28-year-old woman, gravida VII, para IV, AB III, was admitted to an Air Force Hospital on February 10, 1965 for evaluation of progressively increasing shortness of breath and chest pain of several months duration. Just prior to admission, she became orthopneic and developed right upper quadrant abdominal pain. She was diagnosed as having pulmonary hypertension and heart failure. With diuretics, low sodium diet, and bed rest she lost a total of 11 pounds in five days and with this, all signs and symptoms of heart failure disappeared. She was then discharged from the hospital.

One month later she was admitted because of sudden onset of extreme weakness, dizziness, blurred vision, palpitations, cyanosis of the nailbeds, and a tightness in her throat. Physical examination revealed a young Caucasian woman in obvious respiratory distress. Her blood pressure was 100/90 and her temperature was 98.6° F.

Her neck veins were distended and pulsated with a prominent A wave. The lungs were clear. The heart was not enlarged but there was a definite right ventricular heave. There were no significant murmurs, but the pulmonic component of the second heart sound was accentuated. The liver was enlarged 6 cm. below the right costal margin, firm and tender to palpation. There was no peripheral edema.

Chest films revealed an enlarged right ventricle and a prominent pulmonary artery conus which had become progressively enlarged when compared to previous x-rays of January and November, 1964 (Fig. 2). ECG showed right axis deviation and right ventricular hypertrophy (Fig. 3).

The patient again responded to diuretics, low salt intake, digitalis, and bed rest. On March 16, 1965 after her condition became stabilized, the patient underwent right heart catheterization. Her mean pulmonary artery pressure was 100/65 mm. Hg. Careful studies revealed no evidence of a shunt in

Case reports

The occurrence of primary pulmonary hypertension in twins with a review of etiological considerations

Stephen W. Czarnecki, Lieutenant Colonel, MC, USA
*Harvey M. Rosenbaum, M.D.***
*Herbert L. Wachtel, Major, MC, USA****
New York, N. Y.

Primary pulmonary hypertension has been defined as a disease of unknown etiology. The increased pulmonary vascular resistance occurs in the absence of any recognizable lesion in the heart or in the pulmonary parenchyma. The advent of cardiac catheterization procedures has allowed physiologists and cardiologists a means of directly measuring the pulmonary artery pressure. This capability, in turn, has revealed the fact that primary pulmonary hypertension is far from being a rare disease.

A review of published series on primary pulmonary hypertension reveals the fact that many familial cases have been reported.[1-4] Indeed this fact may have some bearing on the etiology. In a hope to shed further light on this aspect, we are reporting what we believe to be the first two cases reported in twins. Both sisters have died and thus we have necropsy confirmation of the diagnosis.

Case reports

Twin B. R. The patient was a 24-year-old Caucasian woman. She was admitted to a hospital in premature labor with vaginal bleeding at 1:30 A.M. on October 9, 1960. Her expected date of confinement was December 14, 1960. Except for some shortness of breath, her prenatal course had been uneventful. On admission to the hospital, she was found to have clinical evidence of an increase in her pulmonary vascular resistance. Specifically, she had a right ventricular heave with increased intensity of the pulmonic component of the second sound. The electrocardiogram (ECG) (Fig. 1) confirmed the right ventricular hypertrophy.

During labor, bleeding was minimal and at 2:40 A.M. the patient was taken to the delivery room where she was given a pudendal block. An amniotomy was performed and spontaneous delivery of a premature female infant occurred at 2:59 A.M.

Shortly thereafter, the patient complained of shortness of breath and was given oxygen by mask and 15 mg. of morphine sulfate intramuscularly. At this time her lungs were clear. Her respirations became more labored and the patient became cyanotic and nonresponsive. An endotracheal tube was passed and her respirations were maintained mechanically. Within minutes, she had no pulse and no heart sounds. The chest was opened and cardiac massage instituted. In spite of all efforts there was no return of cardiac activity. The patient was pronounced dead at 4:00 A.M. on October 9, 1960.

Pathologic report. At autopsy, the heart was found to be enlarged due to a hypertrophied right ventricle. The most striking histologic abnormalities were limited to the pulmonary vascular system

This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.
Received for publication April 19, 1967.
*Formerly Chief of Cardiovascular Service, Letterman General Hospital, San Francisco, Calif. Present address: Chief, Department of Medicine, U. S. Army Hospital, Heidelberg, APO New York, N. Y. 09102.
**Resident in Medicine, Cleveland Clinic, Cleveland, Ohio.
***Chief, Cardiovascular Service, Beaumont General Hospital, El Paso, Texas.

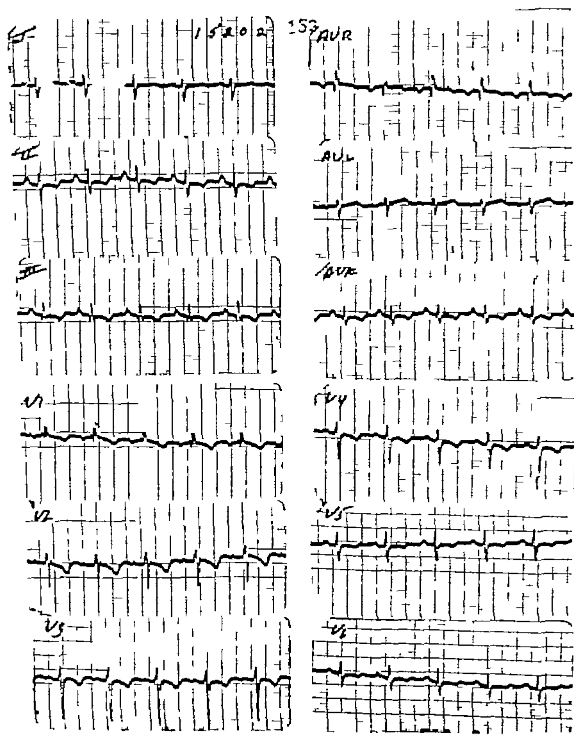


Fig 3 ECG (Twin M. W.) showing right ventricular hypertrophy

Table I. Cases of familial primary pulmonary hypertension

Author	Relationship	Age
Clark and associates	Sister	6
	Sister	7
Dresdale and associates	Mother	43
	Son	21
	Aunt (mother's sister)	31
Van Epps	Brother	6
	Brother	4
Coleman and associates	Brother	41
	Sister	22
	Sister	35
Husson and Wyatt	Brother	4
	Sister	3
Fleming	Mother	?
	Daughter	?
Van Bogaert and associates	Brother	12
	Sister	5
Cohen and associates	Mother	46
	Daughter	20
Boiteau and Libanoff	Sister	28
	Sister	44
Melmon and Braunwald	Sister	30
	Sister	42
	Father	33
	Uncle	17
	Grandmother	33
Parry and Verel	Mother	47
	Daughter	23
	Daughter	25
Rogge and associates	Father	48
	Daughter	18
Present series	Sister	24
	Sister	28

stems directly from the fact that morphologically it is extremely difficult to determine whether the pathologic process is due to embolization or to primary damage of the pulmonary vessels.

Generalized degenerative arteriopathy

Evans and associates pointed out that congenital defects in the media of muscular pulmonary arteries may well be related to the pathogenesis of primary pulmonary hypertension. It was their contention that intimal proliferation occurred over those areas of medial aplasia or hypoplasia and thus proliferation led to arterial stenosis or occlusion and to persistent hypertension.

An exciting and important finding has been reported by James. In a careful study of the arteries supplying the sinus node and the atrioventricular node in three patients who died of primary pulmonary hypertension, he found lesions in these vessels which were similar to those in the pulmonary vessels. Since the arteries supplying both the SA node and the AV node are systemic arteries which were not subjected to abnormal pressures, the possibility arises that the arteriopathy of primary pulmonary hypertension is not solely the result of the elevated pressure. Indeed the changes in the vessels may be part of a generalized degenerative arteriopathy.

Persistence of fetal pulmonary vascularity

It is generally accepted that the most common abnormality in the small pulmonary vessels is a thickened muscular media. Some observers have felt that these vessels may represent a persistence of the muscular type of small arteries and arterioles which are found in the fetus. That such a persistence of fetal arteriolar morphology occurs in some congenital heart defects has been established and the possibility certainly exists that this may be the mechanism of the pathogenesis in some of the cases of primary pulmonary hypertension reported in children.

Increased pulmonary vascular tone

Many observers contend that the basic disorder in primary pulmonary hypertension is one of widespread pulmonary vasoconstriction. This vasoconstriction ultimately leads to the development of structural changes.

To add further weight to the theory that functional spasm rather than obliterative vascular changes are the cause of the pulmonary hypertension, there are the occasional cases in which minimal or no changes in the pulmonary vessels are found at postmortem examination. Shepherd and associates, however, have cautioned that the lesions may be localized and missed entirely if serial sections are not obtained.

In the past few years, the association of Raynaud's disease with primary pulmonary hypertension has been frequently reported.[30-33] This association has served to reinforce the concept that vasospasm may be the initiating factor in the pathogenesis of primary pulmonary hypertension.

That increased vasomotor tone is present in these patients is undeniable. The question which remains unanswered is whether the increased tone with its concommitant increase in pulmonary vascular resistance is the primary event which then leads to the anatomical lesions seen in the vessels.

Bronchopulmonary communications

In 1950 Brinton[34] suggested that abnormal bronchopulmonary communications may in some patients be responsible for causing pulmonary hypertension. Wagenvoort and others[35-37] have noted that in certain cases of severe pulmonary hypertension peculiar vascular formations occur. These vascular bodies have the appearance of glomeruli and thin walled dilated tortuous channels. There is now general agreement that these plexiform structures are not abnormal communications of pulmonary and bronchial vessels.

On the other hand the observations of Wade and Ball[38] would suggest that in certain patients bronchopulmonary anastomotic vessels may play some part in the etiology of pulmonary hypertension. In a very thorough study of ten patients with unexplained pulmonary hypertension they had two patients who differed both clinically and pathologically from the others. Clinically they appeared more cyanotic, complained of hemoptysis, and had biventricular enlargement. In both patients the lung findings revealed large thin-walled bronchopulmonary anastomotic vessels. These were not seen in any of the other cases. The authors postulated that the anastomotic vessels could have been primary, the pulmonary hypertension resulting from the prolonged increase in the pulmonary blood flow, or that these anastomotic vessels could have been an unusual response to obstruction to flow through the pulmonary artery.

Arteritis

An arteritis limited to the lungs in patients with pulmonary hypertension has frequently been observed.[39,40] McKeown[41] has stated that, on a histologic basis, these lesions are identical with polyarteritis nodosa. The relationship of this arteritis to the pulmonary hypertension remains obscure.

Summary

1. Two autopsy proved cases of primary pulmonary hypertension in twins have been reported.

2. The myriad of etiologic considerations of this disease have been reviewed.

3. The repeated observations of this disease in families suggest the possibility of genetic implications in some cases.

4. The etiology of primary pulmonary hypertension continues to challenge the physician. It may well be that there is no one single answer. The increased pulmonary vascular resistance which ultimately produces the entire clinical spectrum of this disease may indeed represent the response of the pulmonary vascular bed to a multiplicity of causes. Review of reported cases strongly suggests this possibility.

REFERENCES

1. Kuida, H., Dammin, G., Haynes, F., Rapaport, E., and Dexter, L.: Primary pulmonary hypertension, Am. J. Med. 23:166, 1957.
2. Shane, S., Aterman, K., Roy, D., and Chandler, B.: Primary pulmonary hypertension. A review and report of five cases, Canad. M. A. J. 91:145, 1964.
3. Heath, D., Whitaker, W., and Brown, J.: Idiopathic pulmonary hypertension, Brit. Heart J. 19:83, 1957.
4. Yu, P.: Primary pulmonary hypertension, report of six cases and review of the literature, Ann. Int. Med. 49:1138, 1958.
5. Clarke, R., Coombs, C., Hadfield, G., and Todd, A.: On certain abnormalities, congenital and acquired, of pulmonary artery, Quart. J. Med. 21:51, 1927.
6. Dresdale, D., Michtom, R., and Schultz, M.: Recent studies in primary pulmonary hypertension, Bull. New York Acad. Med. 30:195, 1954.
7. Van Epps, E.: Primary pulmonary hypertension in brothers, Am. J. Roentgenol. 78:471, 1957.
8. Coleman, P., Edmunds, A., and Tregillus, J.: Primary pulmonary hypertension in three siblings, Brit. Heart J. 21:81, 1959.
9. Husson, G., and Wyatt, T.: Primary pulmonary obliterative vascular disease in infants and young children, Pediatrics 23:493, 1959.

10. Fleming H. Primary pulmonary hypertension in eight patients including mother and her daughter. Australasian Ann. Med. 9:18, 1960.
11. Van Bogaert A., Sutera, J. Tosetti, R. and d'Heer H. Hypertension pulmonaire primitive familiale. Arch. d. mal. d. coeur 54:1185, 1961.
12. Cahen, P. Gonin A. Froment, R., and Dalloz, Cl. Hypertension pulmonaire primitive chez la mere et la fille, Arch. d. mal. du coeur 54:695, 1961.
13. Bostes G. and Libanoff A. Primary pulmonary hypertension, familial incidence, Angiology 14:260, 1963.
14. Melmon K. and Braunwald F. Familial pulmonary hypertension, New England J. Med. 269:770, 1963.
15. Parry W. and Verel, D. Familial primary pulmonary hypertension, Brit. Heart J. 28:193, 1966.
16. Rogge, J. Mishkin, M. and Genovese, P. The familial occurrence of primary pulmonary hypertension, Ann. Int. Med. 65:672, 1966.
17. Wilhelmsen, L. Selander S. Soderholm, B. Paulin, S. Varnauskas, E. and Werko, L. Recurrent pulmonary embolism. Medicine 42:335, 1963.
18. Owen W. Thomas, W. Castleman, B. and Bland, E. Unrecognized emboli to the lungs with subsequent cor pulmonale, New England J. Med. 249:919, 1953.
19. Rosenberg S. A. Study of the etiological basis of primary pulmonary hypertension, Am. Heart J. 68:484, 1964.
20. Barnard, P. Pulmonary arteriosclerosis and cor pulmonale due to recurrent thromboembolism, Circulation 10:343, 1954.
21. Case records of the Massachusetts General Hospital (Case 43311) New England J. Med. 257:235, 1957.
22. Evans, W. Short, D. and Bedford, D. Solitary pulmonary hypertension, Brit. Heart J. 19:93, 1957.
23. James, T. On the cause of syncope and sudden death in primary pulmonary hypertension, Ann. Int. Med. 56:252, 1962.
24. Goodale F. J. and Thomas, W. Primary pulmonary arterial disease, Arch. Path. 58:569, 1954.
25. Wood, P. Pulmonary hypertension with special reference to the vasoconstrictive factor. Brit. Heart J. 20:557, 1958.
26. Short, D. The arterial bed of the lung in pulmonary hypertension, Lancet 2:12, 1957.
27. DeNavasquez, S., Forbes, J. and Holling H. Right ventricular hypertrophy of unknown origin so-called pulmonary hypertension, Brit. Heart J. 2:177, 1940.
28. Scothill, J. A. Case of primary pulmonary hypertension with paralyzed left vocalcord, Guy's Hosp. Rep. 100:232, 1951.
29. Shepherd J. Edwards, J. Burchell H., Swan, H., and Wood E. Clinical, physiological, and pathological considerations in patients with idiopathic pulmonary hypertension, Brit. Heart J. 19:70, 1957.
30. Celoria, G., Friedell, G., and Sommers, S. Raynaud disease and primary pulmonary hypertension, Circulation 22:1055, 1960.
31. Smith W. and Kroop, I. Raynaud disease in primary pulmonary hypertension, J.A.M.A. 165:1245, 1957.
32. Rawson, A., and Woske, H. A. Study of etiologic factors in so-called primary pulmonary hypertension, Arch. Int. Med. 105:233, 1960.
33. Case records of the Massachusetts General Hospital (Case 7-1964) New England J. Med. 270:302, 1964.
34. Brinton W. Primary pulmonary hypertension Brit. Heart J. 12:305, 1950.
35. Wagenvoort, C. The morphology of certain vascular lesions in pulmonary hypertension, J. Path. & Bact. 78:503, 1959.
36. Moschcowitz, E. Rubin, E., and Strauss, L. Hypertension of the pulmonary circulation due to congenital glomoid obstruction of the pulmonary arteries, Am. J. Path. 39:75, 1961.
37. Naeye, R., and Vennart, G. The structure and significance of pulmonary plexiform structures, Am. J. Path. 36:593, 1960.
38. Wade G. and Ball, J. Unexplained pulmonary hypertension, Quart. J. Med. 26:83, 1957.
39. Braunstein, H. Periarteritis nodosa limited to the pulmonary circulation, Am. J. Path. 31:837, 1955.
40. Symmers, W. Necrotizing pulmonary arteriopathy associated with pulmonary hypertension, J. Clin. Path. 3:36, 1952.
41. McKeown, F. The pathology of pulmonary heart disease, Brit. Heart J. 14:25, 1952.

Constrictive pericarditis following acute Coxsackie viral pericarditis

Elliott J. Howard, M.D.
Herbert C. Maier, M.D.
New York, N. Y.

The significant role of viral infections in the etiology of both acute and chronic pericarditis has become manifest in recent years. In most cases, however, the exact nature of the viral infection is poorly demonstrated. Therefore, we are reporting a case of Coxsackie viral pericarditis followed from the stage of acute pericarditis to that of cardiac constriction requiring surgical intervention. The evolution of the Coxsackie B serum titers was traced through the period of pleurodynia, to subsequent acute pericarditis with effusion, and then to constrictive pericarditis.

The term "acute benign nonspecific pericarditis" is often employed in describing cases of suspected but unproved viral etiology. Even more tenuous is the role of viruses as the causative agent of constrictive pericarditis. Christian noted in 1951 that clinicians have regarded the disease with interest and curiosity for more than a century, and Christian himself in 1909 speculated that the failure to find a causative organism in pericardial fluid might be because the organisms (viruses) would not grow on the media being used at that time. A half century later difficulty still remains in identifying the etiologic agent because methods to identify the viruses are not readily available nor simple enough for the clinician to have taken the required specimens at the proper times, most likely because of the lack of methods simple enough to identify the presence of viruses in pericardial fluid and tissue with sufficient frequency to encourage such routine examinations. The problem is illustrated by an epidemic of 48 cases of acute nonspecific pericarditis which were studied for the presence of viruses, but only 5 of these were proved positive. Therefore the term "nonspecific pericarditis" is used when often it is meant to refer to viral pericarditis; some prefer the term "perimyocarditis," which seems justified in view of the electrocardiographic changes and the occasional occurrence of signs of congestive heart failure due to a pericarditis superimposed on an acutely damaged myocardium.

In the case here reported, serologic evidence of the virus, Coxsackie B-3, was present during acute pericarditis. Pericarditis was then observed as it progressed to a constrictive phase in a 14 month period. This is believed to be the first adult case of constrictive pericarditis with evidence of Coxsackie infection proved (serologically) as the cause of the acute process. Of interest was an attack of pleurodynia two years prior to the pericarditis, at which time the presence in

From the Departments of Medicine and Surgery, Lenox Hill Hospital, New York, N. Y.
Received for publication April 4, 1967.

Table I. Coxsackie neutralization titers (pertinent figures only)

Coxsackie strain	8/30/61	9/8/61	11/27/63
B-1	1:40	1:160	1:256
B-3	<1:10	<1:10	1:256

rising high titer of Coxsackie virus of a different type was demonstrated (Table I).

Case report

A 51-year-old white male executive experienced the sudden onset of acute anterior chest pain associated with marked weakness, fainting, and fever on Nov. 6, 1963. The pain was more knifelike than crushing and did not radiate, nor was it related to expiration. The blood pressure was 80/50 mm. Hg, the pulse was 90 per minute, regular and weak. The lungs were clear on examination; the heart sounds were diminished. There were no murmurs or thrills. The ECG showed flattened T waves in all the standard leads compared with the previously normal tracings. The white blood count was 10,050 per cubic millimeter with an increase in small lymphocytes (53 per cent); the erythrocyte sedimentation rate was 73 mm. per hour; serum glutamic oxalacetic transaminase was 13 Sigma units; lactic dehydrogenase was 450 B.B. units; the hemoglobin and hematocrit were normal; the temperature was 100.5° F.

The patient had no previous history of heart disease, but both he and two members of his household had had an acute viral pleurodynia 15 months previously. In each instance, serologic studies demonstrated rising titer of Coxsackie B virus.

The patient was thought to have acute pericarditis rather than myocardial infarction and was kept at rest and given moderate doses of analgesics. The blood pressure returned to previous levels (about 130/85 mm. Hg) in three days, but the lymphocytosis, elevated sedimentation rate, and low-grade fever persisted for three more weeks. During this period T waves were depressed in all leads, and QRS voltage was diminished. There was no ST-segment deviation. A prominent pericardial friction rub was heard during systole at the second, third, and fourth left intercostal spaces at the left sternal border two weeks after the initial symptoms.

Serologic studies of specimens taken three weeks after the acute onset showed significant titers of Coxsackie B-1 and B-3 (Table I). The latter was not elevated following the pleurodynia infection. During the next 8 weeks, the friction rub gradually disappeared and the erythrocyte sedimentation rate and temperature returned to normal. The low QRS voltage and T-wave depression persisted. The heart enlarged slightly and pulsation were slightly reduced. There was slow but progressive improvement over the next five months so that the patient was able to return to part-time work. But two months later fatigue, breathlessness, fullness in the head, and popping of the eyeballs on bending forward became constant complaints. These symptoms became more and more prominent during the next 12 weeks. A loud third sound was present along the left sternal border and the ECG varied very little from the pattern of low voltage and inverted T waves.

One year after the acute pericarditis, signs of increased venous pressure in the upper part of the body were apparent. The face was noted to be slightly swollen. The abdomen became more prominent only shortly before the diagnosis of constrictive pericarditis was made. There was no dependent edema. The antecubital venous pressure was 230 mm. of saline, which increased 20 mm. on deep inspiration (Kussmaul sign). The neck veins were distended at 30 degrees. The systolic blood pressure was 140 to 160 mm. Hg; the diastolic was generally 90 to 110 mm. Hg. Digitalis therapy effected no change in signs and symptoms. Fluoroscopic study showed normal cardiac pulsation and slight left ventricular enlargement. Bacteriologic study and skin tests for acid-fast bacilli were negative.

The impression, now, was that the patient had constrictive pericarditis. Since the symptoms and clinical findings pointed to superior vena caval obstruction as the chief element of the pericardial constriction, a surgical incision (such as midline sternotomy which would give good exposure of this area) was elected. On exposure, minimal cardiac pulsations and marked thickening (3 to 5 mm.) of the presenting portion of pericardium was noted, most marked in the anterior diaphragmatic region and along the right-sided portion of the pericardium extending up over the anterior aspect of the superior vena cava. Over the left ventricle the pericardium was only slightly thickened and was very loosely adherent. Dissection of the presenting pericardium over the right ventricle and the superior vena cava was successfully performed. The adherence was tenacious, and invasion of the myocardium was considerable. Because of marked cardiac irritability when the dissection was carried over the left ventricle, less resection of the left side of the pericardium than usual was deemed advisable in this case. The myocardial irritability was thought to be due to residual myocarditis.

Specimens of resected pericardium were cultured and tested for isolation of Coxsackie virus, but the results were negative. Histologic study revealed fibrosis and chronic inflammation.

The patient made a gradual recovery and returned to full work six months after discharge from the hospital. One year after surgery, the ECG continued to show low QRS voltage and T-wave depression, the heart size was unchanged, and the pericardial knock persisted. Venous pressure was 130 mm. of saline without significant rise on inspiration. The patient continued to tire easily and occasionally felt "fullness in the head," but considerably less than preoperatively. He was able to perform his work and other activities reasonably. It was presumed likely that some constriction and myocardial changes remained, and were the cause

of some of his symptoms. Recently 30 months postoperatively the patient was a ter-skiing vigorously on several occasions without manifestation of cardiovascular disability.

Discussion

Most observers recognize that viruses can and do cause acute pericarditis, but it is not generally appreciated that constrictive pericarditis can be a sequela to the acute viral pericarditis. The present case report may be the first instance of constrictive pericarditis in an adult following acute pericarditis, in which virologic studies give strong presumptive evidence of a Coxsackie virus etiology. A recent report by Gibbons, Goldbloom and Dobell presents a four year-old child who had similar presumptive evidence of Coxsackie B-5 infection concomitant with an acute pericarditis, which rapidly became a constrictive pericarditis in a 4 week period. In this instance as in the case here presented there was a fourfold increase in neutralizing antibody titer within 3 months of the onset of the acute pericarditis.

Christian reports that Levy in 1951 noted no incidence of constrictive pericarditis following acute nonspecific pericarditis in collected cases at the Columbia Presbyterian Medical Center. Carmichael and associates[4] had none in 50 cases followed in some instances, for 10 years and Wood reported that none of his cases of nonspecific pericarditis progressed to chronic constrictive pericardial disease. In a review by Bradley[9] which indicates those studies which should be performed to prove the viral etiology of acute nonspecific pericarditis (neutralizing antibodies, complement fixation isolation of the virus in blood stool and pericardium) there is no mention of constriction as a complication or sequela. It is likely however that as more cases of acute nonspecific pericarditis are studied and as the techniques of virus identification are simplified, more of the cases of constrictive pericarditis will be proved to be of viral etiology. The reports of Rabiner and co-workers, Krook, Blakemore and co-workers, Cooley and co-workers, and Robertson and Arnold include cases which are highly suggestive although without proof of viral origin.

Robertson and Arnold[11] observed 12 cases of acute constrictive pericarditis between 1961 and 1963 of which ten previously had acute nonspecific pericarditis, but had not had virus studies. There had been a Coxsackie viral epidemic in Vancouver in 1960 at that time 125 cases of acute nonspecific pericarditis were admitted to the hospital. Of these, 48 were studied for viral disease but only 5 had a positive stool culture. Although 2 of the 21 cases of constrictive disease were also among these 48 cases they were not among those with positive Coxsackie identification. Krook[8] similarly described 2 of 24 cases of nonspecific pericarditis which progressed to constriction but had not had virus studies. Cooley and associates[1] reported from the Mayo Clinic of 4 patients out of 79 with constrictive pericarditis, who developed their disease after having had acute nonspecific pericarditis. One of the four had three episodes of acute pericarditis at intervals of one and two years, then developed chronic constrictive disease in the fourth year. Connolly and Burchell[12] reporting on the same group of patients, failed to identify viruses in the studies and cultures of fluid and tissues.

Progression may be first suspected by persistence of signs and symptoms of activity. The term benign was applied to acute nonspecific pericarditis, because patients generally recovered completely in six weeks. Most cases of acute nonspecific pericarditis that progress to chronic constrictive disease can be recognized if suspected within one year. The range in time as reported is from four weeks to four years. The course differs from the previously more common tuberculous constrictive pericarditis, in which there is usually an indolent progression for many years. Roentgenograms may show little or no change in heart size. The cardiac silhouette may actually be enlarged and have normal pulsation. Angiography may be of little help since the pericardium is not usually very much thickened.

The diagnosis of constrictive pericarditis may be delayed because of the tendency to reserve that diagnosis for cases with the common clinical features. Although constriction of the ventricles is usually the most significant clinical and pathologic finding in some cases the pericardial thickening may be especially prominent

in a limited portion of the pericardium In such cases a variation from the usual pattern of low cardiac output diminished amplitude of ventricular pulsation low pulse pressure and ascites may be noted This is especially true when the constrictive process is chiefly around the vena cava. In the case reported upon here the clinical manifestations until shortly before operation were essentially those of obstruction to the superior vena cava.

Although it is widely recognized that the most satisfactory operation for constrictive pericarditis includes adequate decortication of the left ventricle when significant myocardial disease is present it is sometimes necessary to modify the surgical approach in the interest of safety Unusual myocardial irritability probably due to residual myocarditis may dictate a more selective and perhaps less routine pericardiectomy for selected cases of viral pericarditis.

The results of surgery for constrictive pericarditis of all types are probably better now than were the good results in 62 per cent of the 415 patients reported upon by Chambliss and colleagues[13] in 1951 Good results imply better cardiac filling increased forward flow reduction of left and right atrial pressure disappearance of fatigue dyspnea ascites, and edema. It should be noted that in many instances regarded as good operative results the venous pressure may not return to normal Kussmaul's sign and the third heart sound (pericardial knock) although softer and later in timing may persist and the ECG and x-ray appearance may remain unchanged Months or occasionally years may pass before the maximum benefit from surgery is seen In order to lessen chronicity Blakemore and co-workers recommend pericardiectomy and cardiac decortication for the relapsing nonspecific pericarditis, and the pericarditis associated with effusion without waiting for constriction to occur

Summary

During a twelve-month period a case of viral pericarditis was observed to progress to constrictive pericarditis. Virology studies disclosed rising titer of Coxsackie B-3 virus antibody

Consideration is given to the current methods of virus identification and the various surgical techniques used to relieve cardiac constriction are discussed A review of recent reports of large series of pericarditis cases is included.

The authors would like to express their appreciation for the advice of Dr. Clarence E. de la Chapelle who saw the patient in consultation The Coxsackie serum neutralization tests were performed by the Department of Health of the City of New York.

REFERENCES

1. Christian H A. Nearly ten decades of interest in idiopathic pericarditis, Am. Heart J 42:645 1951
2. Robertson, R., and Arnold, C R : Constrictive pericarditis with particular reference to etiology Circulation 26:525 1962.
3. Gibbons, J E Goldbloom R. B and Dobell, A. R. C Rapidly developing pericardial constriction in childhood following acute nonspecific pericarditis, Am J Cardiol. 15:863 1965
4. Carmichael, D B., Sprague H. B. Wyman, S. M and Bland, E. F Acute nonspecific pericarditis Clinical, laboratory and follow-up considerations, Circulation 3:321 1951
5. Wood, P Chronic constrictive pericarditis, Am. J Cardiol. 7:48, 1961
6. Bradley E. C.: Acute benign pericarditis, Am. Heart J 67 121 1964
7. Rabiner S F Specter L. S Kipstein, C. B and Schlecker A. A. Chronic constrictive pericarditis as a sequel to acute benign pericarditis Report of a case New England J Med. 251 425 1954
8. Krook, H Acute nonspecific pericarditis Study in 24 cases, including description of two with later development to constrictive pericarditis, Acta med. scandinav 148:201 1954
9. Blakemore W S., Zinsser H F Kirby C. K. Whitaker W B and Johnson, J Pericardiectomy for relapsing pericarditis and chronic constrictive pericarditis, J Thoracic & Cardiovas. Surg 39:26, 1960.
10. Cooley J D Clagett, O T and Kirklin, J W Surgical aspect of chronic constrictive pericarditis A review of 72 operative cases, Ann. of Surg 14 488, 1956.
11. Robertson, R and Arnold, C. T Acute constrictive pericarditis, J Thoracic & Cardiova Surg 49:91 1965
12. Connolly D C. and Burchell, H B. Pericarditis A ten year survey Am. J Cardiol. 7 1961
13. Chambliss, J R Jaruszewski, E J Brofman, B L., Martin, J F and Feil, H : Chronic cardiac compression (chronic constrictive pericarditis) A critical study of 61 operated cases with follow-up Circulation 4:816 1951

Clinical pathologic conference

Alfred P Fishman M.D
Donald Heath M D Ph.D M.R.C.P M C.Path
B L. Pentecost M.D M.R.C.P
Birmingham England

Clinical summary

A 47-year-old toolmaker was admitted to the hospital on Nov 8 1962 with history of blueness since birth. He had been breathless all his life and was unable to play games at school because of this. As a child he fainted on exercise. He had had three attacks of dizziness with blackouts during the past 13 years. During these attacks he experienced headache and weakness of the left arm and leg, and said silly things. For two years he had been breathless at rest. He complained of excessive fatigue. On account of his symptoms he had worked only part time for 10 years and not at all for one year. There was no history of rheumatic fever. He smoked 30 cigarettes a day and drank one pint of beer a day. At examination he was orthopneic and cyanotic and had clubbing of the fingers and toes. His systemic blood pressure was 115/90 mm. Hg and the radial pulse rate was 120 per minute with extrasystoles. The jugular venous pressure was not raised and there was no pitting edema of the ankles or sacral pad. The apex beat was palpable in the midclavicular line in the fifth left intercostal space. There was forcible right ventricular pulsation. A presystolic murmur partially obscured the first heart sound. It was maximal over the left third and fourth intercostal spaces near the sternum but radiated to the apical region where a presystolic gallop was heard. The second heart sound was single. An occasionally loud early diastolic murmur was audible at the lower left sternal edge. There were no adventitious sounds in the chest. There were no abnormal physical signs in the abdomen or in the central nervous system.

During his stay in the ward he complained of abdominal pain. This came on during the night. At first it was intermittent but later it became continuous for 45 minutes. It was mainly umbilical in position. Examination revealed no abdominal distention, no masses, and no guarding. The bowel sounds were normal. He was discharged on Dec 8 1962.

He became increasingly breathless and on July 23 1964 he was readmitted because of a recurrence of his fainting attacks. He was observed during one of these seizures in the ward. He became briefly unconscious and had convulsive movements of the right side of his body. He also had two attacks of severe, cramplike pain involving the lower abdomen. These lasted several hours, and the pain was accompanied by vomiting. He passed melena stools. At 5 A.M. on July 25 he had violent abdominal pain and fainted. He was tender to the left of the umbilicus and in the left loin. There was no rebound tenderness in the abdomen. Three days later he passed dark but not tarry stools. He had a further attack of colicky lower abdominal pain on August 11. He was discharged on August 22.

In January 1966 he had pneumonia at home. Following this his breathlessness increased. He was readmitted on March 7 1966. Physical signs in the chest were unchanged. It was noted, however, that the left femoral pulse was much diminished in amplitude compared with the right.

He was readmitted on Sept. 1 1966 with complaints of pain for 6 months in both legs. The pain was pronounced on exercise. Both legs felt cold. He also had pain for 2 weeks in the chest; he said this came on when he got cold and was relieved by the application of a hot water bottle. His breathlessness was now so extreme that it took him 20 minutes to undress, and he required 5 pillows in bed to sleep. He could walk only 30 yards on level ground. On examination he showed peripheral and central cyanosis. He was orthopneic. His hands were dry and warm. He had clubbing of the fingers and toes. His systemic blood pressure was 110/75 mm Hg. The radial pulse rate was 100 per minute and the rhythm was irregular. The jugular venous pressure was raised to the level of the lobes of the ears. The apex beat was in the anterior axillary line in the seventh left intercostal space. There was right ventricular heave. There was a loud systolic murmur over the

From the Medical School, University of Birmingham, England.
Received for publication May 4 1967.
Address: Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

left lower sternal border and in the region of the apex. This was accompanied by a thrill. Râles were present at both bases. No abnormal physical signs were detected in the abdomen. The left femoral pulse and the pulses below this in the left leg were absent. The right femoral pulse was felt. Both legs were cold and cyanosed.

On September 13 at 1 P.M. he suffered acute retrosternal pain. This lasted for 2 hours and was accompanied by sweating. It did not radiate beyond the chest at first. At 3 P.M. he had pain in the hypogastrium and it continued for 2 days. On examination of the abdomen there was no guarding; no masses were palpable; no urinary symptoms were present. A rectal examination showed no abnormality and caused no pain. The systemic blood pressure remained steady at 110/85 mm Hg. The radial pulse rate was 85 per minute.

He collapsed and died suddenly at 2:50 A.M. on Sept. 14, 1966.

Investigations: The white-cell count was 7 400 per cubic millimeter on July 24, 1964, and 14 200 per cubic millimeter on Sept. 13, 1966. The differential was 54 per cent neutrophils, 1 per cent eosinophils, 41 per cent lymphocytes and 3 per cent mononuclear leukocytes.

Platelets were plentiful.

Erythrocyte sedimentation rate was 1 mm per hour (Wintrobe) on July 24, 1964, and 30 mm. per hour on Sept. 3, 1966.

Serum urea was 27 mg per cent on Dec. 7, 196- and 33 mg per cent on Aug. 31, 1964.

Discussion

DR. FISHMAN: The most striking part of the clinical history of this middle-aged toolmaker is that he was blue from birth. In addition he tired very easily and was short of breath on exercise. His dyspnea became exaggerated so that he was finally orthopneic. His history is punctuated by episodes of dizziness, blackouts and convulsions. From all this, one is confident that he had cyanotic congenital heart disease. This was confirmed when he was seen in 1962 and found to have cyanosis with clubbing of the digits. At that time he had no distension of the neck veins and no abnormal pulsation was noted in them. He had a tachycardia and a narrow pulse pressure with a systemic blood pressure of 115/90 mm Hg, but I don't think we can infer anything of significance from that. However, I note that he had a right ventricular heave, so that one is gradually drawing a picture of cyanotic congenital heart disease with right ventricular hypertrophy without anything to suggest involvement of the left ventricle.

Then we come to "the show-stopper," namely, the second heart sound was single. I will return to that feature subsequently. Associated with this was an early diastolic murmur at the lower sternal edge. This certainly leads us to suspect pulmonary hypertension with insufficiency of the pulmonary valve. At this point I should like to know if he was polycythemic.

DR. PENTECOST: Yes, he was. Here are representative levels of hemoglobin obtained:

	Gm	%
July 24, 1964	19.3	132
March 7, 1966	20.0	137
Sept. 3, 1966	18.9	130

Representative packed cell volumes were:

	%
July 31, 1964	61
Sept. 13, 1966	62

DR. FISHMAN: Well he certainly had high levels of hemoglobin and this leads us to conclude that he probably developed thrombosis. We know, for example, that he passed stools made tarry by blood, and in view of the fact that he also had abdominal pain I think we must consider that he had a mesenteric thrombosis, in either the arteries or veins. Usually, however, such patients have a distended abdomen with constipation and there is no mention of either of these in the clinical history.

Two years later he came back with fainting attacks. These were serious, resulting in unconsciousness and convulsive movements of the right side of the body. He continued to have these attacks but there do not appear to have been any residual effects. One presumes that these were also the result of thrombosis, this time in the cerebral arteries. On the other hand, I feel that it is unlikely that he would be so lucky as to have no residual damage to the brain. An alternative view to account for these attacks would be that he has a mechanism by which he suddenly drops his systemic vascular resistance. Blood flow through the brain decreases. Blood flow through the lung probably diminishes also, so that the blood is not as well oxygenated as usual. Hence there is a diminished perfusion of the brain with poorly oxygenated blood. Then he hits the ground. Gravity comes into play

cerebral perfusion perks up and he gets better

DR. PENTECOST When he came to the hospital in 1964 he gave a history of 3 attacks of unconsciousness with weakness and paresis of the right side of the body He also had abdominal pain, called for a bedpan collapsed on the floor and had convulsive movements of the right side. He was said to have a transient paresis of the right side.

DR. FISHMAN Well the story could be that of cerebral thrombosis. With regard to the abdominal symptoms and the passage of dark stools was there blood in them?

DR. PENTECOST The chemical tests for blood were positive

DR. FISHMAN One thing we must exclude at this point is thromboembolism as contrasted to thrombosis There is nothing in the history or clinical examination to suggest any form of heart disease predisposing to embolism such as subacute bacterial endocarditis. Were blood cultures carried out?

DR. PENTECOST A report on Sept. 9 1966 stated that blood cultures showed no growth after incubation for 10 days.

DR. FISHMAN Well all these results are consistent with the idea that he had cyanotic congenital heart disease with polycythemia and thrombotic phenomena in various parts of the body To proceed in January 1966 he was said to have had pneumonia at home. I wonder if this really was pneumonia or thrombosis in a pulmonary artery? At this point I should like to see some ECGs and radiographs of the chest to exclude Fallot s tetralogy

(At this point were shown ECGs taken on Nov 30 1951 (Fig 1) Nov 1 1962 June 25 1964 and Sept. 10 1966)

These ECGs indicate right ventricular hypertrophy with pulmonary hypertension. Leads V_1 and aV$_R$ are certainly consistent with right ventricular hypertrophy Looking at the earliest ECG though I wonder if there isn t a suggestion of left ventricular hypertrophy as well?

DR. PENTECOST I agree with you that all these ECGs show evidence of sinus rhythm with a few ventricular extrasystoles, a slightly positive axis, and a partial right bundle branch block pattern. There is certainly evidence of right ventricular hypertrophy

DR. FISHMAN After looking at these ECGs, I am sure we are heading in the right direction. Let us see the chest radiographs.

Chest radiographs taken on Nov 10 1962 July 24 1964 and Sept. 2 1966 were shown at this point.)

These radiographs (Fig 2) show right ventricular enlargement and a prominent pulmonary conus, features consistent with a severe degree of pulmonary hypertension. This film excludes a diagnosis of Fallot s

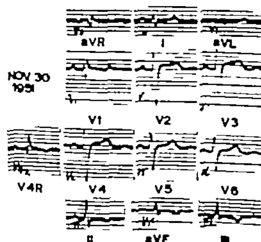


Fig. 1 ECG taken on Nov 30 1951



Fig 2. Chest radiograph taken on Sept. 2, 1966.

tetralogy. There is incidentally no evidence of a pulmonary infarct.

DR. PENTECOST: The radiographic appearances of the aortic knuckle suggest that there is a right-sided aortic arch. Do you agree?

DR. FISHMAN: Yes, I do, but that is not part of my story! (Laughter.) Well, finally we come to the story of his chest pain. This is not surprising in view of his propensity to thrombosis. His retrosternal pain and final sudden collapse was almost certainly due to coronary thrombosis, although other possibilities are pulmonary infarction and pneumonia.

Similarly, the symptoms in his left leg are almost certainly related to thrombosis in the major arteries to this limb. The palpation of the apex beat over to the left suggests that the heart dilated towards the end of this patient's life.

In conclusion, I think there are three outstanding problems: the nature of the congenital heart disease, the single nature of the second sound in the pulmonary area, and the systolic murmur reported as being present.

I believe he had cyanotic congenital heart disease with right ventricular hypertrophy and pulmonary hypertension secondary to a large intracardiac shunt. He also had a right-sided aortic arch. In other words, this patient's diagnosis fits into the category of the Eisenmenger syndrome with pulmonary arterial pressure at systemic level. It seems to me that he had a ventricular septal defect, as in the original case of Eisenmenger, but he could have had another type of congenital defect. He might even have been a case of primary pulmonary hypertension, but of course this is really a disease of young women and not middle-aged men. We can exclude Fallot's tetralogy with certainty.

How can we explain the single second pulmonary sound? One can hear two sounds in the second left interspace: the first is aortic and the second pulmonic. One way to produce a single sound at the base is to have a common ventricle with two major vessels arising close together from it. There will be virtually simultaneous closure of the semilunar valves. In the present patient there was, I believe, a large ventricular septal defect so that the two ventricles were acting like a single ventricle with a common ejectile force. Furthermore, the blood pressure in the pulmonary and systemic circulations must have been very similar. Leatham[1] has written on this subject.

Under these circumstances of equal resistances in the pulmonary and systemic circulations there could have been little flow across the shunt, so that I am puzzled by the systolic murmur and thrill that were present over the left lower sternal border and in the region of the apex. I suppose this could be explained by mitral incompetence, but I doubt it. Similarly, there was no real evidence of tricuspid incompetence.

DR. PENTECOST: Would you like to see the findings at cardiac catheterization in 1962? The levels of pressure and oxygen saturation in the various cardiac chambers are shown in Table I.

DR. FISHMAN: There is a jump in oxygenation in the infundibulum of the right ventricle; this indicates the presence of a ventricular septal defect. This is the slight increase I would expect with nearly equal resistances in the pulmonary and systemic circulations and a balanced shunt. We could also have pin-pointed the site of the defect by visualizing directly the course of the catheter. Angiocardiography or dye dilution curves would also help.

This whole clinical picture is very similar to that originally described by Eisenmenger in a young man of 32 years with a high ventricular septal defect and an overriding aorta. One may find reference to this original case at the beginning of

Table I

Site	*BP (mm Hg)*	*O saturation (per cent)*
Main pulmonary artery	100/30	68
Right ventricle (infundibulum)	95/0	66
Right ventricle (body)	95/0	62
Low right atrium	0	62
High right atrium	0	63
Superior vena cava		59
Inferior vena cava		59
Left brachial artery	100/70	83

Wood's[14] Croonian Lectures on the subject of the Eisenmenger syndrome.

PROF. ARNOTT What was the pattern of his final illness?

DR. FISHMAN I think a terminal arrhythmia from his coronary thrombosis. Of course, patients with this syndrome often have a fatal hemoptysis, but there is no evidence of this in the present case.

DR. HEATH The form of congenital heart disease present was a high ventricular septal defect in the region of the pars membranacea septi. This was large with a diameter of 2.5 cm. and an area of 4.9 cm. Because the surface area of the subject's body was 1.75 m.², the area of septal defect could be expressed as 2.8 cm. per square meter of total body surface area. Most clinical physiologists accept that a ventricular septal defect exceeding 1.0 cm.² per square meter is of hemodynamic significance in producing pulmonary hypertension. Hence the defect in the present case is consistent with the production of severe pulmonary hypertension. There was slight overriding of the ascending aorta so that the congenital heart lesion is consistent with the diagnosis of Eisenmenger's complex. The aorta was right sided as suggested by the radiographic appearances.

The heart was enlarged and weighed 520 grams, (the upper limit of normal is 350 grams). The right ventricle was hypertrophied and was 10 mm. thick (normal 4 mm.). At this center we are skeptical of the validity of the classical measurements of the thickness of the right ventricle and prefer to weigh the free wall of this chamber. In this case, it weighed 154 Gm., the upper limit of normal being 65 Gm. These features are consistent with the presence of severe pulmonary hypertension, since there was no pulmonary stenosis. In view of Dr. Fishman's suggestion from the ECG that the left ventricle might also be enlarged, it is of interest that this chamber proved to be slightly hypertrophied weighing 220 Gm. (upper limit of normal 185 Gm.). The left ventricle was dilated and there was severe myocardial disease so that in spite of its increased weight its thickness was only 10 mm. The ratio of left ventricular to right ventricular weight was 1.4 (normal ratio 2.5 to 3.5) indicating isolated right ventricular hypertrophy secondary to pulmonary hypertension. The circumferences of the tricuspid (13 cm.), mitral (11.5 cm.) and aortic (7 cm.) valves were normal. There was no evidence of dilatation and incompetence of the tricuspid valve. The pulmonary valve was incompetent, its circumference being 9.5 cm.

The major pulmonary arteries were dilated and atheromatous. A section of the pulmonary trunk, whose media was almost as thick as that of the aorta, showed an aortic configuration of elastic tissue; this showed that the pulmonary hypertension in this case had been present from birth.

Postmortem angiograms were prepared



Fig. 3. Elastic pulmonary artery showing medial hypertrophy and atherosclerosis. (Elastic Van Gieson stain. ×35.)



Fig. 4. Parent muscular pulmonary artery occluded by intimal fibroelastosis with two thin-walled vein-like branches. (Elastic Van Gieson stain. ×150.)

from the right lung. The injected radiopaque medium showed a "pruned tree" appearance indicating occlusive pulmonary vascular lesions.

The left lung was inflated and fixed by the formalin-steam method of Weibel and Vidone. This prevents distortion and collapse of the small pulmonary blood vessels. Histologic examination of the vasculature of the lung showed Grade 5 hypertensive pulmonary vascular disease. Elastic pulmonary arteries showed medial hypertrophy and atheroma (Fig. 3). The muscular pulmonary arteries showed severe intimal fibroelastosis with fibrous atrophy of the underlying media. Some occluded arteries had thin-walled branches arising proximal to sites of occlusion which looked like veins (Fig. 4). Such appearances have been erroneously regarded as arteriovenous anastomoses but Brewer[4] has conclusively demonstrated that such thin-walled branches are entirely arterial in nature and represent a collateral blood flow to the pulmonary capillary bed. Numerous angiomatoid dilatation lesions were also present (Fig. 5). These are merely more complex arrangements of the thin-walled vessel described above and have the same functional significance. Some of these had ruptured to give rise to pulmonary hemosiderosis. All these appearances were typical of Eisenmenger's complex with hypertensive pulmonary vascular disease. As Dr. Fishman has indicated, such pulmonary vascular lesions are associated with a severely elevated pulmonary vascular resistance of fixed organic basis.[7] This increased vascular resistance is irreversible even after surgical correction of the defect which led to their development.[8]

A second group of abnormalities was found in the heart. The origin, course, and distribution of the coronary arteries were normal but both coronary arteries were severely atheromatous. The left main coronary artery showed gross atheroma with calcification and ulceration. The right main coronary artery was occluded by a recent coronary thrombosis. In addition to this acute thrombosis there was widespread myocytolysis indicative of chronic coronary arterial insufficiency. It is likely that Professor Arnott had a sense of *déjà vu* in looking at these slides since he took part in the first of this series of clinicopathologic conferences where this condition was discussed. The affected myocardial fibers show a vacuolated appearance but the reticulin framework in the myocardium remains intact (Fig. 6). Among the affected muscle fibers are mononuclear cells and macrophages. (The reader is referred to the previous report for a full description of the condition.) Finally, there was an extensive area of dense grayish fibrosis in the region of the apex and in the anterior part of the interventricular septum due to healing of a previous myocardial infarct. This area measured 5 by 3 cm. and overlying it was a mural thrombus. Thus the heart showed an acute coronary thrombosis, a healed myocardial infarct, and myo-

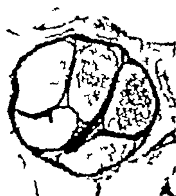


Fig. 5. Angiomatoid dilatation lesion. (Elastic Van Gieson stain × 235.)



Fig. 6. Myocardial muscle fibers showing myocytolysis. (Hematoxylin and eosin stain × 450.)

cytolysis indicating chronic coronary arterial insufficiency

As well as the mural thrombus overlying the healed infarct there was antemortem thrombus in the right atrial appendage. There was much thrombus in the dilated atheromatous pulmonary arteries It may be that this was autochthonous, but it is equally possible that it was the result of organization of pulmonary thromboemboli. In addition there was extensive antemortem thrombus in the atheromatous abdominal aorta. This was 8.5 cm. in length and extended from just below the origin of the renal arteries to 2 cm. above the aortic bifurcation. There was also thrombus in the left common iliac artery and in the left femoral artery Clearly these thrombotic phenomena in the coronary and aortic systems accounted for the angina and the symptoms in the left lower limb

A careful examination was made of the intestines and their blood supply No mesenteric thrombus was present but it seems almost certain that such thromboses were the cause of his severe and repeated abdominal symptoms.

Similarly at necropsy there was no thrombus in the cerebral arteries and there was no evidence of cerebral softening However it seems certain that small thrombotic lesions were responsible for the cerebral symptoms.

The kidneys weighed 390 grams. They showed multiple acute infarcts which were probably brought about by thromboembolism from mural thrombus in the left ventricle or from thrombus in the abdominal aorta.

These findings agree very closely with the clinical analysis of Dr Fishman. However in spite of his excellent discourse I would like to take issue with him over his use of Paul Wood's term the Eisenmenger syndrome. Although this term was introduced by a distinguished British cardiologist I personally think it is unfortunate that it has achieved such widespread acceptance When one remembers that Eisenmenger in 1897 described a case of ventricular septal defect with overriding aorta it seems quite inappropriate to use such a term to describe entities like atrial septal defect.

DR. FISHMAN I never use this term in the United States! I agree with you that the name is wrong but at the same time the idea is right. From the practical standpoint it is valuable to have a succinct term like this to include all the diseases that present the virtually identical clinicopathologic picture of congenital heart disease with reversed shunt. At the bed side it is often impossible to diagnose precisely the underlying cardiac anomaly but one can diagnose the syndrome I would like to see someone come up with a name that excludes the name Eisenmenger but which groups all these patients with this clinicopathologic syndrome together

DR. PENTECOST Dr Heath what is your view of the clinical physiology of this case One would imagine that in view of this large intracardiac shunt that he must have had a high pulmonary vascular resistance from fetal life. Yet now there seems to be a lot of divided opinion as to whether one can really have a congenital Eisenmenger situation.

DR. HEATH Well Wagenvoort[12] in Amsterdam has certainly shown that in ventricular septal defect with pulmonary hypertension in the first month of extra uterine life there is an involutionary regression in medial thickness of the small pulmonary arteries. Only subsequently after the eighth week, do these vessels show a secondary increase in medial thickness. Later still there is a development of intimal fibrosis and dilatation lesions such as we have seen today

DR. FISHMAN Do you believe that there is a congenital abnormality of the pulmonary blood vessels in Eisenmenger's complex to accentuate the effect of the ventricular septal defect in producing elevated pulmonary vascular resistance

DR. HEATH No I don't think there is. This hypothesis of a retention of a fetal-type pulmonary vasculature is of course closely associated with the name of Dr Jesse E. Edwards[1] but I think he has been very much misunderstood as to what he implied I am sure that he meant us to understand that normally in the fetus the pulmonary arteries are thick walled in association with a physiologic pulmonary hypertension. Usually the blood vessels

become thin with the precipitate fall in pulmonary arterial pressure at birth In those infants with large ventricular septal defects the pulmonary arterial pressure remains high and the pulmonary arteries remain thick walled In other words this is a *normal* response of *normal* pulmonary arteries to *abnormal* stimuli The same response of constriction of normal pulmonary arteries to the abnormal stimulus of chronic hypoxia at high altitudes will also result in a thick walled pulmonary vasculature

DR. FISHMAN It seems odd however that pulmonary arteries can regress in this manner and then show a subsequent thickening in the face of unremitting pulmonary hypertension

DR. HEATH I am convinced that such an initial regression of medial thickness occurs in the pulmonary arteries Wagenvoort s studies were carried out meticulously I should like to see similar detailed hemodynamic data obtained over the period of time when these vascular changes occur Are we sure that the pulmonary hypertension is maintained at the same high level May there not be a falling away of pulmonary arterial pressure in the period when the vessels show this initial thinning?

Dr Fishman what do you think about the reported development of infundibular pulmonary stenosis or even closure of ventricular septal defect that is said to occur in Eisenmenger s complex Have you any experience of these changes having occurred

DR. FISHMAN I don t think there is any doubt that such lesions develop in a few cases of ventricular septal defect However at the same time I should like someone to show that the clinical course of a patient with a ventricular septal defect 5 cm in diameter like the one we have seen today can be modified by such mechanisms. I find that difficult to believe

DR. PENTECOST Is there a place for repeated phlebotomy in these patients?

DR. FISHMAN Yes provided one carries out repeated small phlebotomies of about 200 ml of blood at a time If you remove too much blood at one time say 500 ml some of these patients tend to develop a thrombosis Heparin or other anticoagulants may also be used The results are not over-gratifying but at least you keep them alive and don t have the temptation to subject them to surgery—which is, of course a major cause of death in patients like this with a reversed shunt.

DR. HEATH It is interesting to note just how long some of these patients survive when they are not subjected to surgery Last year we performed a necropsy on a woman of 35 years who had a persistent truncus arteriosus with dilated pulmonary arteries arising directly from the truncus.

DR. CUMMING I was interested to see what a close relation there was in this case between thrombosis and atheroma of the affected artery

DR. HEATH I agree but it is difficult to be sure of the significance of this.

Diagnosis

Eisenmenger s complex with widespread thrombotic manifestations.

REFERENCES

1 Arnott, W M Heath D and Howell, J Clinical-pathologic conference focal injury tolysis in aortic stenosis, AM. HEART J 60 139 1960
2 Brewer D B. Fibrous occlusion and anastomosis of the pulmonary vessels in case of pulmonary hypertension associated with patent ductus arteriosus, J P th. & Bact. 70:299 1955
3 Ed ards, J E. The Lewis A. Conner memorial lecture. F nctional pathology of the pulmonary vascular tree in congenital cardiac disease, Circulation 15 164 1957
4. Eisenmenger V: Die angeborenen Defecte der Kammerscheidewand des Herzens, Ztschr klin Med. 32 (suppl): 1 1897
5 Fulton, R. M H tchinson, E. C., and Jones, A. M Ventricular weight in cardiac hypertrophy Brit. Heart J 14:413, 1952.
6. Heath D and Ed ards, J E. The pathology of hypertensive pulmonary vascular disease Circulation 18:533 1958.
7 Heath, D Helmholz, H F J Burchell, H B DuShane, J W and Edwards, J E. Graded pulmonary vascular changes and hemodynamic findings in cases of atrial and ventricular septal defect and patent ductus arteriosus, Circulation 18 1155, 1958.
8. Heath, D Helmh tz, H. F J Burchell, H B DuShane, J W Kirklin, J W and Edwards J E.: R lation bet een structural hanges in the small pulmonary arteries nd the immediate reversibility of pulmonary h perten ion following closure f entricular nd tri l septal defects, Circulation 18 1167 1958.
9 Heath, D Wood, F H D Shane J W nd Edwards, J E.: The structure of the pulmonary trunk at different ages and in cases of pul-

monary hypertension and pulmonary stenosis, J Path. & Bact. 77:443 1959
10 Hicken, P Evans, D and Heath D Persistent truncus arteriosus with survival to the age of 38 years, Brit. Heart J 28:284 1966
11 Leatham, A. The second heart sound. Key to auscultation of the heart, Acta cardiol. 19:395 1964.
12 Wagenvoort, C. A., Neufeld, H. N DuShane J W and Edwards, J E. The pulmonary arterial tree in ventricular septal defect. A quantitative study of anatomic features in fetuses, infants and children, Circulation 23 740, 1961
13. Weibel, E. R. and Vidone, R A Fixation of the lung by formalin steam in a controlled state of air inflation, Am. Rev Resp. Dis 84:856, 1961.
14 Wood, P The Eisenmenger syndrome, or pulmonary hypertension with reversed central shunt, Brit. M J 2 701 755 1958.

Programmed vectorcardiography
The ST T loop in the horizontal plane



Agustin Castellanos Jr M D
Louis Lemberg M D
Louis Salhanick M D
Miami Fla

In the Meno one of the famous dialogues by Plato we see Socrates teaching a boy some of the elementary principles of geometry not by lecturing on them but by eliciting them from the boy with the aid of diagrams. This is the starting point of the Socratic philosophy of teaching as well as of the principles of modern Programmed Instruction. The theory presupposes that with the right schematic diagrams and with pertinent questions the teacher can lead the student to understand a universal proposition Very little information is given for if the thoughts of the student are focused on the diagrams in the proper way the brain by its own effort will produce the correct answer from within The thoughts seem to originate in a subconscious storehouse of truth The facts are reached by personal insight to which the pupil has been simply stimulated by the teacher

The program presented here is some-

From the University of Miami School of Medicine Section of Cardiology and the Division of Electrophysiology Jackson Memorial Hospital, Miami, Fla.

Presented at the 16th Annual Scientific Session of the American College of Cardiology Washington, D. C., Feb. 16 to 19, 1967

Received for publication April 3, 1967

what elementary and oversimplified so it is best suited for beginners. We recognize that vectorcardiography should usually be taught as a whole through the analysis of all planes and loops rather than as the study of the isolated ST T loop in the horizontal plane. However it is believed that, by concentrating on the repolarization loop some additional information will be gathered which will surely enhance the student s understanding of vectorcardiography in general.

Programmed Instruction as applied here complements conventional teaching Time and simplicity are important considerations at any level of learning so we have planned a quick and easy method that will improve comprehension and retention. Over the years, various methods of teaching clinical vectorcardiography have been tried Programmed Instruction is only one of them The response to this course" will help in deciding if it is worthwhile to explore and expand in this direction

For all of you who are not familiar with this type of teaching it is important to know that the material is presented in small steps or frames. Each frame requires an active response. Immediately after writing your response it should be checked with the correct answer which is given at the right.

You should not look at the answers until you have written down your own impression. We recommend that the answers be covered and then exposed one at a time. Be careful not to expose the next answer

PART 1

Normal ST T loop in the horizontal plane

1 In scalar electrocardiography it is customary to separate the repolarization phase of the ventricles into an ST segment and a T wave This distinction can also be made from the vector cardiogram However in the latter the ST and T vectors merge to form a single geometric figure referred to as the ST T loop

Thus, in the vectorcardiogram the ST T loop represents ventricular ________

repol rization

2. Before proceeding further let us review the spatial parameters of the horizontal plane

Posterior

Right ———————— Left

Anterior

3 (a) Let us further divide the horizontal plane into four quadrants

Right posterior quadrant (RPQ) Left posterior quadrant (LPQ)

————————

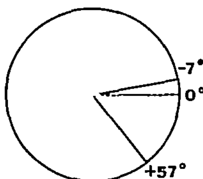
Right anterior quadrant (RAQ) Left ant rior quadrant (LAQ)

(b) In which quadrant are the following ST T loops located? (b) LPQ

(c) LAQ



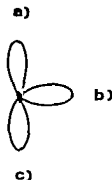
4 (a) The spatial orientation of the normal ST T loop ranges from −7° to +57° (In the horizontal plane.)



(b) Are the following ST T loops normal or abnormal? In which quadrants are they located? (b) abnormal, RPQ (c) abnormal, RAQ



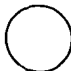
(c) Which of the following ST T loops is normal and which abnormal according to their *orientation?* (a c) abnormal (b) normal



5 (a) The ST T loops are usually elongated and fusiform Rarely they are moderately rounded The *shape* of the ST T loop is indicated by the length to-width ratio. This ratio varies from infinite to 2.6 Values below 2.6 are considered abnormal.



(b) Is the following ST T loop normal or abnormal? (The length-to-width ratio is 1) — bnormal



(c) Loops with length-to-width ratios under 2.6 are called *round* or *circula*

(d) Circular ST T loops are seen in the following
   (1) ischemia
   (2) ventricular hypertrophy—uncomplicated
   (3) conduction defects
   (4) digitalis therapy
   (5) rarely in normal cases with tachycardia or autonomic imbalance

(e) Hence a circular ST T loop at normal heart rates is most probably (normal, abnormal) — abnormal

(f) The significance of a circular ST T loop is clear (true, false) — false

(g) The following ST T loop is (normal, abnormal) in orientation and (normal abnormal) in shape — normal, abnormal



6 (a) The QRS loop and the ST T loop normally have the same type of rotation. Since the rotation of the QRS loop is C-CW what is the *rotation* of the ST T loop (Remember we refer here only to the horizontal plane.) — C-CW

(b) There are times in which the repolarization loop is so elongated that an almost linear type of inscription results. In rare instances there is some degree of crossing over of both limbs.





C-CW rotation (usual) Linear (rare but normal) Figure 8 (rare but normal)

(c) Note that the *arrow indicates* the *sense of rotation*. An arrow drawn within the ST T loop indicates the sense of ________ rotation

(d) Some normal individuals with minor degrees of right sided conduction disturbances may have ST T loops with CW rotation (Examples incomplete right bundle branch block pattern $S_1 S_2 S_3$ syndrome or late activation of the crista supraventricularis.)

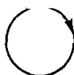
(e) One can therefore say that in otherwise normal individuals minor nonspecific conduction disturbances could produce a normal abnormal rotation (CW) of the ST T loop abnormal

(f) Check the abnormalities, if any of the following ST T loops



	N	Ab	
a) orientation	(__)	(__)	abnormal
b) shape	(__)	(__)	normal
c) rotation	(__)	(__)	normal

1



	N	Ab	
a) orientation	(_)	(__)	abnormal
b) shape	(__)	(__)	abnormal
c) rotation	__)	(__)	abnormal



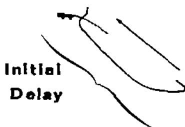
	A	Ab	
a) orientation	(__)	(__)	abnormal
b) shape	(__)	(__)	norm l
c) rotation	(__)	(__)	abnormal

7 (a) Repolarization is slower at its onset than during its terminal stages. Therefore, the initial portions of the ST T loop will be more delayed than the terminal parts. This area of normal delay will be indicated on the vector cardiograph by a closer lineup of the "dashes. (In the spatial vector loops illustrated n this course each dash" *represents 2 5 msec.)*

(b) In these records each dash in the ST T loop represents _____ msec. 2.5

(c) Dashes which are very close together in their line up indicate a (slow/fast) speed of inscription. slow

(d) The in tial part of the ST T loop is called the efferent or centrifugal limb and is inscribed at a slower speed The terminal part of the loop is called afferent or centripetal limb and is inscribed at a faster speed



(e) The initial part of the ST T loop is inscribed at a (*faster slower*) speed than the terminal part. slower

9 (a) But in the ischemic ST T loop both initial and terminal parts will show a similar speed of inscription (no answer required)

(b) Answer true or false

—The orientation of the normal ST T loop ranges from −7° to +57° (__) (T)

—A circular ST T loop is always normal. (__) (F)

—If the dashes nto which the loops are subdivided are closer together than usual this means that the corresponding part of the loop is delayed (__) (T)

—The term nal part of the ST T loop is inscribed at a slower speed than the initial part. (__) (F)

10 (a) Check the norm l or abnormal features of this ST T loop



	N	Ab	
a) orientation	( )	( )	(N)
b) shape	( )	( )	(N)
c) rotation	( )	( )	(N)
d) speed of inscription	( )	(_)	(N)

(b) Check the normal or abnormal features of this ST T loop



	N	Ab	
a) orientation	( )	(__)	(A)
b) shape	( )	(__)	(A)
c) rotation	(_)	( )	(N)
d) speed of inscription	(_)	(_)	

The magnitude of the ST T loop ranges from 0 10 mv to 0 55 mv

( ) Which of the following ST T loops are normal and which are abnormal

a) 1 11 mv	(_)	abnormal
b) 0 01 mv	(_)	abnormal
c) 1 01 mv	(_)	abnormal
d) 0 51 m	(_)	normal
e) 0 11 mv	(__)	normal

11 (a) The magnitude of the ST T loop will not be stressed further nor w ll another measurement the QRS-T angle be emphasized in this course because the direction of the maximal QRS vector is needed to evaluate the angle In this presentation we are concerned mainly with the ST T loop

(b) The normal QRS-T angle should not exceed 40°

(c) Are the following QRS-T angles normal or abnormal?

a) 100° (_) b) 30° (__) c) 70° (__) a) Ab b) N c) Ab

d) 15° (__) e) 0° (__) d) N, e) N

PART II

The abnormal ST T loop in the horizontal plane

All ST T loops located outside the 57° to −7° range are abnormally oriented Let us classify the abnormal repolarization loops

primarily by their orientation without neglecting the fact that abnormalities in other parameters may or may not be present.

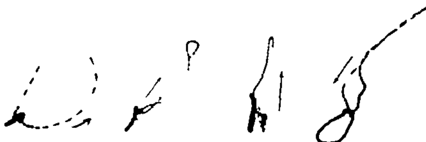
(A) *The ST T loop located in the right anterior quadrant* (*RAQ*)

Which is the right anterior quadrant (RAQ)?

---

1 The ST T loop can be affected by alterations in the process of depolarization. These are called secondary changes since they depend on an altered pathway of depolarization.

2 "Secondary ST T loops located in the RAQ are seen in the following



LVH & Strain CLBBB RV pacemaker W-P W type B

Note that in all these cases the ST T loops are oriented in the RAQ

3 IN LVH or LBBB the ST loop usually shows a normal (C CW) rotation.



(a) In LVH the presence of CW rotation suggests associated ischemia, aortic stenosis, or severe hypertrophy



10 (a) Check the normal or abnormal features of this ST T loop



	V	16	
a) orientation	( )	( )	(N)
b) shape	( )	( )	(N)
c) rotation	( )	( )	(N)
d) speed of inscription	( )	( )	(N)

(b) Check the normal or abnormal features of this ST T loop



	V	16	
			(N)
a) orientation	( )	( )	(A)
b) shape	( )	( )	(A)
c) rotation	( )	( )	(N)
d) speed of inscription	( )	( )	

The magnitude of the ST T loop ranges from 0 10 mv to 0 55 mv

(c) Which of the following ST T loops are normal and which are abnormal

a) 1 11 mv	( )	abnormal
b) 0 01 mv	( )	abnormal
c) 1 01 mv	( )	abnormal
d) 0 51 mv	( )	normal
e) 0 11 mv	( )	normal

11 (a) The magnitude of the ST T loop will not be stressed further nor will another measurement the QRS-T angle be emphasized in this course because the direction of the maximal QRS vector is needed to evaluate the angle. In this presentation we are concerned mainly with the ST T loop

(b) The normal QRS-T angle should not exceed 40°

(c) Are the following QRS-T angles normal or abnormal?

a) 100° ( ) b) 30° ( ) c) 70° ( ) a) Ab b) N, c) Ab

d) 15° ( ) e) 0° ( ) d) N, e) N

PART II

The abnormal ST T loop in the horizontal plane

All ST T loops located outside the 57° to −7° range are abnormally oriented Let us classify the abnormal repolarization loops

7. These are 2 variations of the ischemic ST T loop



In one (left) the initial and terminal portions appear to be inscribed at the same speed. In the other one (right) there is an early delay (which does not last for the duration of the whole afferent or centrifugal limb as in normal cases). This short area of delay is followed by uniform speed of inscription of the rest of the loop.

(a) A loop showing uniform speed of inscription is called an ________ ST T loop — ischemic

(b) In the ischemic ST T loop differences in speed of inscription are (as marked as/less marked than) in the normal ST T loop — less marked

(c) Ischemia very frequently produces CW rotation (no answer required)

(d) Which one is the normal and which the ischemic ST T loop?



A



B

	N	Ab	
A	(__)	(__)	(A) N
B	(__)	(__)	(B) Ab

Note that the ischemic ST T loop shows an initial very slow rate of inscription but that the rest of the efferent and all of the afferent portions of the loop are inscribed at the same speed.

8. Check the normal or abnormal features of this ST T loop



	N	Ab	
(a) orientation	(__)	(__)	(A)
(b) rotation	(__)	(__)	(N)
(c) shape	(__)	(__)	(A)
(d) speed of inscription	(__)	(__)	(N)

9 An unusual type of ischemic T loop is the one in which the initial part is slowed and is followed by an area of faster conduction and a final delayed terminal portion of the loop Check other abnormalities if any In this loop



	N	Ab	
(a) orientation	(_)	(_)	(A)
(b) rotation	(_)	(_)	(A)
(c) shape	(_)	(_)	(A)

10 An ST T loop which shows a terminal delay is (normal/abnormal) abnormal

(B) *Let us now consider the ST T loop in the right posterior quadrant (RPQ)*

1 Which quadrant is right posterior (RPQ)? RPQ

2 (a) ST T loop in RPQ can be due to secondary changes in repolarization as in some cases of W P W type A



Note the initial QRS delay typical of W-P W

(b) It is important to consider that uncomplicated ventricular strain (left or right) will not show ST T loops in the RPQ

(c) In which quadrant was the ST T loop of LVH and strain located? (In this case the ST T loop is opposed to the QRS loop.) RAQ

3 The following are primary causes of ST T loop locations in the RPQ (a) ischemia, (b) pericarditis, and (c) digitalis.

4. Study this loop



(a) Is the orientation normal or abnormal | abnormal

(b) Is the rotation normal or abnormal? | abnormal

(c) Does it show uniform speed of inscription? | yes

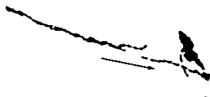
(d) Would you call it ischemic? | yes

Study this loop



(e) It was obtained from a digitalized patient. Note that the loop is open (this means that there are significant ST segment changes) Also observe that part of the loop is in the RPQ and part in the LAQ These changes are very commonly seen with digitalis.

5 (a) This patient has LVH Are the ST T loop and the J vector typical of LVH and strain? | No



(b) In what quadrant is this ST T loop located? (_) | RPQ

(c) The abnormal ST T loop in LVH and strain is located in the _____ quadrant. | RAQ

6. Check the normal or abnormal features of this ST T loop



	V	Ab	
(a) orientation	(_)	(_)	(A)
(b) rotation	(_)	(_)	(N)
(c) shape	(_)	(_)	(N)
(d) speed of inscription	(_)	(_)	(N)

(C) *The abnormal ST T loop in the left posterior quadrant* (*LPQ*)

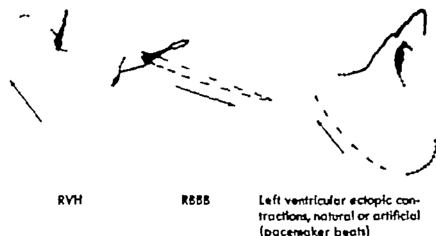
1 Which one is the left posterior quadrant?

2 (a) Not all loops in the LPQ are abnormal

(b) Those between 0 and $-7°$ might be normal especially in young adults.

(c) Hence only loops between $-7°$ and $-90°$ will be considered abnormal in orientation

3 Secondary changes in repolarization with loops in the LPQ are observed in



RVH RBBB Left ventricular ectopic contractions, natural or artificial (pacemaker beats)

4 (a) The ST T loops in RVH and strain and CRBBB are located in the ____ quadrant LP

(b) Whereas, the ST T loops in LVH and strain and CLBBB are located in th ____ quadrant RA

5 Primary changes in repolarization in the LPQ are seen in anteroseptal ischemia



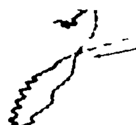
(a) In which quadrant is this ST T loop located? LPQ

(b) Is its rotation normal? yes

(c) What is the normal rotation in the horizontal plane? C-CW

(d) Does it show uniform speed of inscription? yes

6 Check the normal or abnormal features of this ST T loop



	N	Ab	
(a) orientation	(__)	(__)	(A)
(b) shape	(__)	(__)	(N)
(c) rotation	(__)	(__)	(N)
(d) speed of inscription	(__)	(__)	(A)

Check the abnormalities, if any of the following ST T loop



	N	Ab	
(a) orientation	(__)	(__)	(N)
(b) shape	(__)	(__)	(A)
(c) rotation	(__)	(__)	(N)
(d) speed of inscription	(__)	(__)	(N)

Would you believe that this loop was obtained from a patient with pure LVH and "strain"? (__) no

Would you believe that this loop was obtained from a patient with anteroseptal infarction (__) yes

Would you believe that Programmed Vectorcardiography enhances the ease with which you learn the subject? (__) We hope it does

You have now completed a programmed course on "The ST T loop in the horizontal plane" It was designed with the purpose of facilitating comprehension and retention of the morphologic aspects of the repolarization loop an area of vectorcardiography often disregarded We hope that this short course has been of some help. Although it has not been conclusively proved that programmed instruction will increase retention of the learned material we believe that this parameter can be enhanced if the facts are presented in a simple fashion as an appropriate stimulus and learned through motivation of the student at his own pace.

REFERENCES

1 Portrait is from painting by Raphael (Vatican Museum)
2 Taylor A E Socrates The man and his thought, New York, 1953, Doubleday Anchor Books
3 Lysaught, J P and Williams, C M A guide to programmed instruction, New York, 1963, John Wiley & Sons, Inc
4 Silverberg S M A quantitative study of the Frank vectorcardiogram A comparison of younger and older normal populations, Am. J Cardiol. 18:672 1966
5 W Jurczuk, W J nd Burch, G E. Analyses of the T E loop in normal subjects of different ages, Am. J Cardiol 10:507 1962
6. Chou, T Helm, R A nd Lack, R The significance of ide T E loop, Circulation 30:400, 1964
7 Hoffman, I T ymor R and Kitell, I T loop rotation i ischemic heart disease Hoffman, I editor Vectorcardiography 1965 Amsterdam, 1966, North Holland p. 181
8. Castellanos, A J Lemberg, L., Salhanick, L., and Gomez, A. The morphology of the ST T loop in healed myocardial infarction, Dis Chest 50 113, 1966.
9 Haraml, K., Mashima, S Sato, C., Hanoi, Y and Meda, H. A study of the direction of inscription of the vectorcardiographic T loop in left and right ventricular hypertrophy J p. Heart J 4:386, 1963.
10. Grishman, A., and Scherlis, L. Spatial vectorcardiography Philadelphia, 1962, W B Saunders Company

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

The treatment of cardiogenic shock

V. The use of corticosteroids in the treatment of cardiogenic shock

*Ronald H. Dietzman, M.D.**
*Richard C. Lillehei, M.D., Ph.D.***
Minneapolis, Minn.

Extensive laboratory and clinical research has established the use of corticosteroids in massive doses as an accepted form of treatment of septic shock. Their value in cardiogenic shock has been less clear. Much of the controversy is emotionally tinged and detailed experimental or clinical studies are scarce.

Originally, the rationale for the use of cortisol in shock was for adrenal replacement or supplementation. We know that adrenal hypofunction in shock is rare and in fact, the blood levels of the naturally occurring cortisol in shock are usually elevated.

The response to glucocorticosteroids in experimental and clinical septic shock has been demonstrated to be dose-related and the principal measureable effect of massive doses in this situation is a reduction of peripheral vasoconstriction and peripheral resistance. Moreover, evidence is now accumulating that steroids help maintain the integrity of cell membranes and subcellular particles such as lysosomes. The evidence for these cell sparing effects of corticosteroids are not as well documented as their hemodynamic actions.

We indicated in an earlier article in this series that the hallmark of cardiogenic shock is peripheral vasoconstriction and reduced tissue perfusion. These hemodynamic events result from a fall in cardiac output and blood pressure after the myocardial damage has reduced the inotropic function of the heart. This, in turn, affects the baroreceptors which stimulate release of the catecholamines epinephrine and norepinephrine from the adrenal medulla and sympathetic nerve endings. The catecholamines stimulate α receptors in adrenergically sensitive arterioles and venules, resulting in vasoconstriction and reduced tissue perfusion in the lungs, kidneys, splanchnic viscera, and skin.

Glucocorticoids in massive doses will reduce this vasoconstrictive response which also occurs in septic shock. The mechanism of this change is not clear. The steroids have not been shown to specifically block the α receptors. Yet we can empirically measure a decrease in peripheral resistance in man and in the dog when glucocorticoids are given in massive doses. In the past, most investigators have been disappointed with the effect of glucocorticoids in cardiogenic shock. A careful look at these reports however, shows that the doses used were small and designed for replacement therapy rather than for a pharmacological or mass effect. When given in this manner vasoconstriction is changed little, if at all.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn. 55455.
Supported by United States Public Health Service Grant HE05941.
Received for publication Sept. 14, 1967.
*Sterling Winthrop Research Fellow.
**Professor of Surgery.

In contrast changes in peripheral resistance are marked when the dosage of glucocorticoids is large and this is best illustrated in the dog. Here we have produced a diffuse myocardial infarction by embolization of the coronary arteries by microspheres. After the infarction there is an immediate and sustained fall in cardiac output and blood pressure, resulting in intense vasoconstriction and a marked increase in the total peripheral resistance. This vasoconstriction is present in all regions of the body but it is most marked in the adrenergically sensitive splanchnic, renal and cutaneous beds. Renal blood flow is depressed and urine output decreases. Myocardial blood flow also decreases, but not to the same extent as the renal and intestinal flows. The myocardium actually receives a greater percentage of the cardiac output during shock reflecting the relative insensitivity of the coronary circulation to changes in catecholamine concentrations. With the persistence of vasoconstriction tissue perfusion is reduced and anerobic metabolism ensues. All this throws a greater work load on an already damaged myocardium. This change from aerobic to anerobic metabolism is reflected by the rising serum lactic acid levels. To compensate for the lactic acidosis, the dog hyperventilates and reduces its serum pCO_2. With the persistence of vasoconstriction the myocardium gradually fails and death occurs in the majority of these dogs with myocardial infarction within the first 24 hours. Only 25 per cent survive longer than three days. Methyl prednisolone

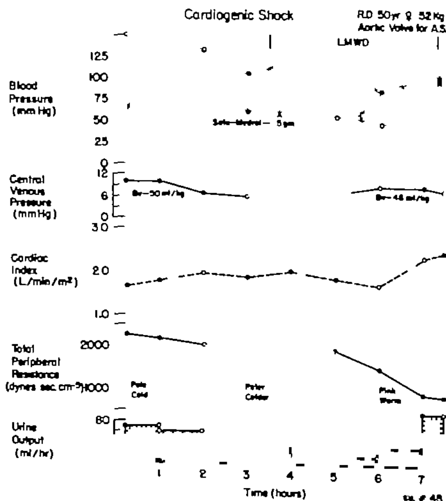


Fig. 1

sodium succinate (Solu Medrol) given after the myocardial infarction and vasoconstriction have occurred significantly improves survival by reducing vasoconstriction. Total peripheral resistance falls, renal blood flow and urine output increase, lactic acid levels fall, and pCO_2 rises as the stimulus to hyperventilation is withdrawn. All of this results in a more equitable redistribution of the diminished cardiac output and a general over-all improvement in tissue perfusion. With an intravenous dose of 15 mg. per kilogram of methyl prednisolone the disturbances are ameliorated but do not return to normal. Survival increases 25 to 40 per cent. A more striking change occurs with the administration of 30 mg. per kilogram of methyl prednisolone. The hemodynamic and biochemical changes associated with the infarction return almost to the normal range and survival increases to 65 per cent, a figure comparable to that achieved by the most potent α adrenergic blocking agent, phenoxybenzamine.

The mechanism for the reduction of the vasoconstrictive response in shock by the glucocorticoids is still unknown, but our observations show that their effect is dose related exactly as previously seen in septic shock. Similar results have been achieved with a comparable dose of dexamethasone phosphate (Decadron) 6 mg. per kilogram and hydrocortisone sodium succinate (Solu-Cortef) 150 mg. per kilogram. Each of these steroids appear to have a beneficial effect in cardiogenic shock in direct proportion to its ability to decrease the peripheral vasoconstrictive response accompanying the myocardial damage. With these

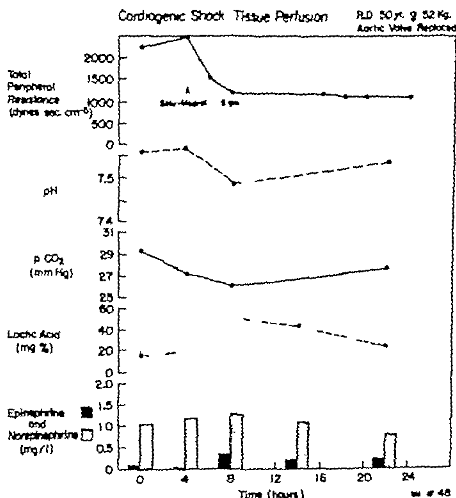


Fig. 2

experimental observations as a basis, we have used massive doses in patients suffering cardiogenic shock. Figs. 1 and 2 depict the course of a 50-year-old woman in cardiogenic shock after replacement of an aortic valve for aortic stenosis. The cardiac index was markedly reduced and the patient maintained her blood pressure by peripheral vasoconstriction. This vasoconstriction could be qualitatively observed by a falling urine output and increasing pallor and coldness of her extremities and quantitatively as an elevated total peripheral resistance. At this time the plasma norepinephrine levels were markedly elevated. The increased plasma levels of lactic acid reflected the reduction in flow in the vasoconstricted areas. The patient compensated for this lactic acidosis by hyperventilation and consequently her serum pCO_2 was reduced. Within 1½ hours of the administration of 30 mg. per kilogram methyl prednisolone as a single intravenous bolus, along with low molecular weight dextran to maintain her central venous pressure at 10 mm. Hg there was a dramatic increase in the patient's cardiac output, and a fall in her total peripheral resistance. Clinically, her extremities became warm and pink and her urinary output rose to 80 ml. per hour. The circulating catecholamine levels decreased simultaneously. As the vasoconstriction relented and tissue perfusion improved, the lactic acid washed out of these tissues and subsequently fell to within normal limits. Concomitantly, the pCO_2 rose as the stimulus for hyperventilation was withdrawn. The patient subsequently recovered and was discharged from the hospital.

We have observed similar results from massive doses of glucocorticoids in other patients suffering cardiogenic shock. To emphasize the vasodilation of the steroids, patients have been given blocking doses of phenoxybenzamine after the steroids with no further decrease in total peripheral resistance. This therapeutic trial established that maximum vasodilatation had been achieved by these massive doses of glucocorticoids.

We have not seen any adverse effect from such large doses of methyl prednisolone, dexamethasone or similar substances if they are given in the following fashion in patients suffering cardiogenic shock. Methyl prednisolone (Solu-Medrol) 30 mg. per kilogram, dexamethasone phosphate (Decadron) 6 mg. per kilogram or hydrocortisone sodium succinate (Solu-Cortef) 150 mg. per kilogram is given as a single intravenous bolus. The effect of the steroid is occasionally observed within the first 5 minutes as a marked increase in the cardiac output but the peak effect occurs at about 1½ to 2 hours. The steroid is only given if the central venous pressure is over 10 cm. H_2O. If the pressure is lower than this, volume replacement in the form of blood, plasma, or low molecular weight dextran is first tried. The choice of the volume expander depends upon the hematocrit. Dextran is preferred because of its osmotic diuretic effect upon the kidneys and its hypertonicity which attracts a volume of fluid from the extravascular space almost equal to itself. If the patient continues in shock 4 hours after this therapy, a continuing search for other reasons for perpetuation of the shock picture is made. Most often this is due to unrecognized infection, bleeding, infarcted viscera, or combinations of these problems. The advantage of the use of steroids is the need of only a single intravenous injection, no need for a continuous intravenous drip, smooth vasodilatation and increased vascular capacitance, making volume replacement less hazardous in cardiogenic shock.

Finally, the availability of the glucocorticoids to all physicians also recommends their use in contrast to the difficulty of most in obtaining α-adrenergic blocking drugs such as phenoxybenzamine.

REFERENCES

1. Shubin, H., and Weil, M. H.: Failure to confirm the pressor effect of corticosteroid hormones in the treatment of circulatory shock, Circulation (Suppl. II) 32:196, 1965.
2. Bloch, J. H., Dietzman, R. H., Pierce, C. H., and Lillehei, R. C.: Theories of the production of shock, Brit. J. Anaesth. 38:234, 1966.
3. Sambhi, M. P., Weil, M. H., and Udhoji, V. N.: Acute pharmacodynamic effects of glucocorticoids, cardiac output and related hemodynamic changes in normal subjects and patients in shock, Circulation 31:523, 1965.
4. Spink, W. W.: Endotoxic shock, Ann. Int. Med. 57:538, 1962.
5. Lillehei, R. C., Dietzman, R. H., Movius, S., and Bloch, J. H.: Treatment of septic shock, Mod. Treatmen 4:321, 1967.

Atheroembolism; a late complication of arteriosclerosis

Coronary, cerebral, and peripheral scular diseases are well recognized omplication of arteriosclerosis The recent l er ture emphasizes the frequency of old phenomenon observed by pa thologist namel heroembolism haracterized by the presenc of small cholesterol cry tals in one or mult ple organs of the bod in patients w th a severely therosclero ic aorta. Nowada s, there is little doubt hat these holesterol cry tals come from dislodgeme t of theromatous plaques lo ted the aort and ts main branches. This represents the lat tage of arteriosclerosis olving the large arteries which the ulceration of atheromatou plaque w th the discharge of mor phou eosinophilic material and holesterol crystals to variou organs and tissues seems t be the ex plana ion of he clinical feat res of theroembolism.

Although he symptoms may be related t any organ, they frequen l produc recognizable clinical pattern Presen ng manifest tions which should arouse suspicion of this entity nclude (1) paroxysmal and ischemic changes of the feet and legs, livedo reticulares and gangrene despite adequate arterial pulses (2) hypertension and im paired renal f nction (3) abdom nal pain, gastrointestinal hemorrhage and pancreat tis (4) occasional neurologic mptoms nd retinal emboli, and (5) myocardial infarction or coronary insuf ficiency -6

In a recent publication 5 cases were described in four of which muscle biopsy from the lower extremities proved to be luable diagnostic aid Leukocytosis with neutrophilia, elevated sedi mentation rate, azotemia, lbuminuria, and melena were frequently present

This syndrome occurs almost exclusively in the elderly Diabetes, syphilis and gout seem to play an important role as predisposing factors.

The diversified ymptomatology explains the multiple terms pplied to this syndrome, diff se arteriopathy 7,8 purple toe syndrome, and cholesterol embolization, but those titles are misleading because we are not describing a primary disease of the rteries or pure cholesterol emboli but atheromatous embolism which happens to contain holesterol

The unanswered question in atheroembolism is, how t treat this cond tion Prevention of arteriosclerosis nd its ssociated hypercholesterolemia nd hyperglyceridemia should be the main aim In this regard the se of diets nicotinic acid nd estrogens leaves much t be desired Do anticoagu lant help or worsen this condition? Clinical obser tions and some experimental work seem t demon strate that the latter possibility is more likely by f oring the dislodgement of theromatous ma terial from the damaged and eroded arterial wall. These studies are not yet extensive enough for satis factory interpretation and more work in this field is needed before any definitive conclusion could be reached.

Jorge A. Carrajal M.D
Veterans Administration Hospital
Long Beach Calif

REFERENCES

1 Carraj l J A t al. Atheroembolism an etiologic factor in renal insufficiency gastrointestinal hemorrhages and peripheral vascular disease, Arch. Int. Med. 119:593, 1967

2 Eliot, R S., Ka J h, V l and Edwards, J E. Atheromatous embolism, Circulation 30:611 1964.

3. Hollenhorst, R. W : Vascular status of patients who have cholesterol emboli in retina, Am J Ophth. 61 1159 1966.

4. Porter W B., and V ughan, E. W : Coronary embolism. A complication of syphilitic aortitis. Report of 3 cases, Am. J M Sc. 200 184 1940.

5 Evans, W Diffuse arteriopathy Brit. Heart J 21 703 1962.

6. Moldveen-Geronimus, M and Merriam, J C., Jr Cholesterol embolization from pathological curiosity t clinical entity Circulation 35:946 1967

Origin of blood supply to sinoauricular and atrioventricular node

Knowledge of the origins of the blood supply to the sinus node and the atrio-ventricular node has increasing practical significance today because of the more frequent surgical approach to the base of the heart. We have studied 192 hearts by means of postmortem coronary artery injections and careful dissection. The origins of the sinus node artery and the atrioventricular node artery have been determined. In addition we have determined the origin of the vessel descending in the posterior interventricular sulcus (the posterior descending artery) in the same group.

Material and methods. The selection of case material for postmortem examination was largely random process, but a significant number of patients were selected because of previous history of heart disease. Cannulae were tied into the right and left coronary arteries at their origin. The coronary bed was flushed with saline for 10 minutes, after which the coronary arteries were filled with barium gelatin mass similar to that described by Schlesinger but with the use of barium sulfate of smaller particle size (Micropaq). The injection was carried out at room temperature for a period of 20 minutes at pressure of 100 mm. Hg. The injection mass did not pass through the capillary bed, and never emerged from the venous channels. The heart was cooled to hasten solidification of the injection mass, and stereoscopic anteroposterior and lateral radiographic exposures were made at 40 inch tube film distance. These radiographs served as a guide for detailed dissection of the large coronary vessels, which was carried out after 24 hours of fixation in 10 per cent formalin. The arteries were carefully observed and the origins of the sinus node artery and atrioventricular nodal artery noted. Also noted was the origin of the posterior descending artery. The origin of the sinoatrial node artery was observed in 186 cases, the origin of the atrioventricular nodal artery in 189 cases, and the origin of the posterior descending artery in 190 cases.

Picker X-ray Corporation, White Plains, N. Y.

Results and discussion. The sinus node artery was found to arise from the right coronary in 60.8 per cent and from the left circumflex coronary artery in 37.6 per cent (Table I). In three hearts there were two vessels, one arising from the right coronary artery and the other from the left circumflex coronary artery supplying the sinus node; however the vessel from the left was the larger in all three instances. There was no difference between Caucasians and Negroes and an insignificant difference between the sexes. This is similar to James' findings, although he found a slightly greater percentage originating from the left.

The sinus node artery usually arises within the first 3 cm. distal to the origin of the left circumflex or the right coronary artery. However, in 7 (10 per cent) of the origins from the left circumflex, the sinus node artery arose as the distal extension of the superior remnant of the left circumflex rather than from the proximal segment. In these cases, the sinus node artery passed posterior to the atrial appendage and across the roof of the atrium to reach the sinoatrial node at the base of the superior vena cava. James[2] described this variation in two hearts. Similarly, the usual origin of the sinus node artery from the right is within the first 3 cm.; however, in 4 (3.5 per cent) cases the sinus node artery was found to arise distally just proximal to the origin of the posterior descending artery. From this origin it coursed superiorly over the atrial roof to reach the sinoatrial node.

The origin of the blood supply to the atrioventricular node is predominantly from the right, with 84.7 per cent originating from this artery and only 15.3 per cent from the circumflex artery (Table II). There is no racial difference. Female patients have an even greater frequency of origin from the right coronary artery with 93.75 per cent compared to 80 per cent in male subjects. This further substantiates the suggestion of Schlesinger[4] and James[2] as to the sexual variation. The over-all findings of blood supply to the atrioventricular node are similar to those of James.

Table I. Origin of sinus node blood supply

	Total		Male		Female		Caucasian		Negro		Indian
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	
Right	113	60.8	76	62.3	37	57.8	78	62.9	36	59	—
Left	70	37.6	44	36.1	26	40.6	45	36.3	23	37.7	—
Both	3	1.6	2	1.6	1	1.6	1	.8	2	3.3	1
Totals	186		122		64		124		60		?

Table II Origin of atrioventricular node blood supply

	Totals		*Male*		*Female*		*Caucasian*		*Negro*		*Indian*
	N	*Per cent*	N	*Per cent*	N	*Per cent*	N	*Per cent*	N	*Per cent*	
Right	160	84 7	100	80	60	93 75	109	84 5	51	85	1
Left	29	15 3	25	20	4	6 25	20	15 5	9	15	
Totals	189		125		64		129		60		1

Table III Origin of posterior descending artery

	Total		*Male*		*Female*		*Caucasian*		*Negro*		*Indian*
	N	*Per cent*	N	*Per cent*	N	*Per cent*	N	*Per cent*	N	*Per cent*	
Predominant right	154	81	97	77	57	89 1	106	82 2	47	78 3	1
Predominant left	30	15 8	25	19 8	5	7 8	19	14 7	11	18 3	
Balanced	6	3	4	3 2	2	3 1	4	3 1	2	3 3	
Totals	190		126		64		129		60		1

The origin of the posterior descending artery is almost always the same as the origin of the atrioventricular node artery (Table III). The right coronary artery continued as the posterior descending in 81 per cent, while the left circumflex formed the posterior descending in 15.8 per cent. This latter figure is slightly greater than the 10 per cent found by James.[2] In 6 instances (3.2 per cent) there were dual vessel supplying the posterior wall and both coursed the length of the posterior wall. Again, sexual variation was noted similar to that reported by James, with 89.1 per cent arising from the right in female subjects compared to 77 per cent in male patients.

Summary. A total of 192 hearts has been studied by postmortem coronary artery injection and the origins of blood supply to the sinus node, atrioventricular node, and posterior descending artery determined. The artery to the sinus node was found to originate from the right in 60.5 per cent and from the left in 38 per cent, with 1.5 per cent from both. The artery to the atrioventricular node was from the right in 84.7 per cent and from the left in 15.3 per cent. The origin of the posterior descending artery was from the right in 81 per cent and from the left in 15.8 per cent, with dual supply in 3.2 per cent. Female subjects have an even greater frequency of origins from the right side, with the atrioventricular nodal artery occurring from the right in 93.75 per cent and the posterior descending artery as a continuation of the right coronary in 89.1 per cent.

Donald H. Rembolt, M.D.
Donald B. Hackel, M.D.
E. Harvey Estes, Jr., M.D.
Departments of Medicine and Pathology, Duke University Medical Center
Medical Service, Durham Veterans Administration Hospital
Durham, N. C.

Dr. Rembolt was supported by United States Public Health Service Training Grant No. HE-05369. Dr. Hackel is the recipient of United States Public Health Service Career Research Award No. HE-K6-14 188. This work also received support from the following grant: T12 HE-5736, and a grant from the A.M.A. Committee for Research on Tobacco and Health (Dr. Estes).

REFERENCES

1. Schlesinger, M. J.: New radiographic mass for vascular injection, J. Clin. & Lab. Invest. 6:1, 1937.
2. James, T. N.: Anatomy of the coronary arteries, New York, 1961, Hoeber Medical Division, Harper & Row Publishers, Inc.
3. Schlesinger, M. J.: Relation of anatomic pattern to pathologic conditions of the coronary arteries, Arch. Path. 30:403, 1940.

The classification of coronary artery fistulas

If w are t speak of entities in disease there must not be names, nor even our concepts, but the things—the th g Thompson and the thing Williamson i certain phases of their being

—*Sir Thomas C Albutt 1896*

U til 20 years ago, developmental anomalies of the coronary arterial circulation ere solely of academic interest and documentation thereof made on the basis of topsy findings. Bjork and Crafoord's[1] fortuitous discovery and successful treatment of such pathologic ent ty t operation ushered in the contemporary preoccupation th these lesions. I addition t sporadic case reports of nusual ani ts there are now av ilable large mulatn series and review on the subject. Of the sundry categories of oronary ascular berrations fistulas ha received the most attention because of heir read menability to definitive surgical correction

It was na oidible in iew of he vast disparity of coronary angiomatous fistula t pes, that classifications be proposed to id in the nderstanding of their genesis, kinetic and semelogy. Steinberg, Baldwin, and Dotter[4] made distinction between tw types on the basis of fetal maldevelopment Type I resulting from defectiv different tion of oronary capillary lements and Type 2 in which there existed anomalous origin of coronary artery ith oncomita intercoronary communication arising from defect n formation of the primitiv bulbar septum. Edwards[5] decried he segregation of oronary arterial anomalies on ana omic grounds pointing ou that the most important bad for common denominator distincti f nctional hunting mechanisms M n[6] suggested the succinc descriptiv phase *corona rteriov nceal fistula* for communication between oronary artery and ardiac chamber and that the term *coronary arteriovenous* wa rum be reserved for abnormal condu ts between oronary artery nd the coronary eins or sinu Swan and co-workers nd l p-ha categorized the lesions ac ording t he source nd recipient structure of he fistulou track or ith respect to coincidental ardiac defec Sw emphasized that, for larity of sema the term *arteriovenous fistula* should be restricted ommunic tion between coronary artery nd ein and ha connection between coronary artery nd pulmonary artery should be called an *arteriovarterial fistula* A recen lassific ion, tendered by Lied hen, Lalleberg and Cappelen ubdi ded fistulas into tw groups according hemodynamic sequelae T pe I emptying into he pulmonary in or lef side of the heart and T pe empty in he righ side of he heart or pulmonary artery The former are not detected by righ heart he eriza ion nd the increased strain is confined he left entricle I the la ter ariety disclosed and me surable by right heart catheteriza ion he m seil rre la ory load of the shunt is imparted to he right entricle and pulmonary vascular bed I ber Gale and Lam described nine differe arieties j in the categors of *coronary arterial fistulas ending in the heart chambers*. Effler and his associates,[10] who ha the largest series of surgically treated coronary fistulas t date, proposed the following classification based on anatomic features

Group I Abnormal origin of major artery or branch

1. Left coronary artery arising from pulmonary artery
   a. Antegrade flow right-to-left shunt no collaterals
   b. Retrograde flow left-to-right shu t with collaterals
2. Left circumflex branch arising from pulmonary artery
   a. An egrade flow right-to-left shunt no collaterals
   b. Retrograde flow left-to-right shu t, with collaterals
3. Left anterior descending branch arising from pulmonary artery
   a. Antegrade flow right-to-left hunt no collaterals
   b. Retrograde flow left-to-right shunt, with collaterals
4. Right coronary artery arising from pulmonary artery
   a. A tegrade flow right to-left shunt, no collaterals
   b. Retrograde flow left-to-right shunt, with collaterals

Group B Normal origin abnormal dra age of major artery or branch to pulmona arter right ventricle right atrium oronary us or superior vena ava.

1. Left mai coronary artery to right side of heart
2. Left anterior descending oronary artery t right side of heart
3. Left circumflex oronary artery to right side of heart
4. Right coronary artery t right side of heart
5. M ltiple origins

Admittedly there is much meri in trying t establish an orderly arrangement in all the characteristics of particular disease entity Nevertheless, as ider documentation of coronary artery fistulas has accrued, it has become correspondingly eviden tha no single nosologic system is sa isfactory or complete Some malforma ions rtually def lassification on ei her teleologic grounds or structural configuration Much dispute centers on the significance of localized or diffuse coronary aneurysmal hanges in the etiopathogenesis of fis ulas and arguments are still raised periodically relevant t the direction of flow in hese hannels. I is plain that the classific ions hich has been proferred until now suffer from either oversimplification or the con erse The principal irtue of Effler classification is that it least is realistic in encompassing almost ll possible combina ions As an increasing number of postt matic oronary ascular fistulas are re-

corded there will doubtless be proposed f rther subdivision of the lesions to genital nd acquired t pes

The ol ject lesson h h is ga ned from examining the liter ture is that as might be expected oronary rtery fist las and kindred aberrations need not be divorced from the general head ng of Abnormalities of the oron y vascular Each ndi idual lesion warrant comprehensi description i both qu l tativ nd quantitativ term since the surgeon ltimatel ignore neither anatom fact nor ph siologic data This goal be achieved pre operativ ly by thorough t liz tion of fl possible diagnostic modalitie t one disposal includ ng ardiac catheterization par meters nd selecti coronary arteriograph nd cineangiograph Add tional measurement made t oper tion an id further haracterization of the lesion and d t t the technical maneu ers t be employed for tha par ticular case [*] W ha found, from personal experienc that present classific tions of coronary rtery fist las are more de act ng tha usef l nd rely exclusi l on the aforementioned guidelines for surgic l management

David Chas Schechter M D
Department of S rgery
New York Medical College
New York N Y

*Fellow of he Varnack Foundation

REFERENCES

1 Bjork, V O nd Crafoord C Arteriovenous neurysm of the pulmonary artery sim lating patent ductus arteriosus Botalli, Thorax 2:65 1947
2 Steinberg I Bald in J S and Dotter C T Coronary arteriovenou fist la, C rculation 17:372, 1958.
3. Ed ards, J E Anomalous coronary rteries th pecial reference t arteriovenous-lik communications, Circulation 17 1001 1958
4 M C S Coronary arterior-cameral fist la, Brit Heart J 22:374 1960
5 Sw n, H Wilson, J N Woodward, G and Blount S. C Surgical obl teration of coronary art ry fistula to right entricle Arch Surg 79:820 1959
6 Upshaw C B J Congen tal coronary arteriovenou fist la Report of case with analy of 73 eported es Am H r J 63 399 1962
7 S n, H Discu ion Surgery 61:49 1967
8 Dedichen, H Skalleberg I nd Cappelen. C J Congenital coronary artery fist la, Thorax 21 121 1966
9 T ber R. F Gale H H nd Lam C R Coronary rtery-right heart fi tulas, J Thoracic & Cardiovas Surg 73:84 1967
10. Effler D B Sheldon, W C Turner J J nd Groves, L K C ronary rteriovenous fi tula Diag osis nd surgical management Report of 15 ses, Surgery 61:41 1967
11 Zuhdi, N Kr ft D Carey J and Greer A. Coronary arteriovenous-lik comm nications, Arch Surg 80 178 1960
12 Hudson, R I B Cardiovascular pathology Baltimore, 1965 The W lliam & Wilkin Compa y Vol 1 pp 621-634
13 Summerall, C P Lee W H nd Bonne J N I tracardiac h ts after penetrating wound of the heart New England J Med 272:240 1965
14 Jones, R C and J h ke E J Coronary arter -atrioventricular fist la nd entricular septal defect due t penetr t ng ound of the he rt Circulation 32:995 1965
15 Sarot I A, nd Schechter D C Post tr umatic coronary rteriovenous fist la Surv I nd surgical cure I press
16 Sabiston, D C J Pelargonio, S and T ussig H B Myocardial inf rction in inf ncy The surgic l management of complication of congen tal origi of the left oronary artery from the pulmonary artery J Thoracic & Cardiovas Surg 40:321 1960
17 Hallma G L Cooley D A nd Singer D B. Congen tal nomalies of the coronary arteries natomy pathology and surgical treatment Surgery 59 133, 1966.

Prolapse of the posterior leaflet of the mitral valve
Chromosome studies in three sisters

Recently there ha e been reports th literature[1] indicating that the auscultatory finding of lat systolic m rmu associated with mid or lat systolic click is du t prolapse of the posterior leaflet of the mitral al int the left tri m ith mitral regurgitation occurring lat systole It has been suggested that there is familial incidence of this cond tion nd, in prev iou report from this department f milial incidence as found in t families. I one family three sisters had ery similar auscultatory findings namely mid-systolic lick nd late systolic murmu One as investigated by means of hemodynamic studies and left ventricular angiography nd was how t ha prolapse of the posterior leaflet of the m tral alv nd m tral regurgitation

As congenital abnormalities ha been show sometimes t be associated w th chromosome abnormalities chromosome studies ere performed in these three sisters, it being presumed that they all ha the same cardiac bnormality

Chromosome spread of peripheral blood leu kocyte cult res were prepared by modification of the techniqu of Moorhead and associates. From each culture 30 cells were cou ted t metaphase spread nd 6 of these were photographed and nalyzed All counted nd analyzed cells showed normal female hromosome complement. N

numerical nor structural abnormalities were seen.

Congenital malformations vary considerably in type and aetiology. The disease may be inherited by chromosomal abnormalities or single gene defects, or environmental factors may produce the disorder without genetic influence. Cardiac malformations are a feature of a few conditions associated with chromosomal abnormalities, such as Down's syndrome and some cases of Marfan's syndrome. A few families have been reported in which hereditary cardiac malformations are present, but in general there is not a strong tendency for congenital heart malformations to aggregate in families. Generally genetic factors seem to be important because the concordance rate of cardiac malformation is low for monozygotic and dizygotic twins. The negative findings in these three sisters exclude the presence of a chromosome abnormality although a genetic cause is likely.

Mary Sta nard M.B. B.S.
Cardiac Department, Royal Melbourne Hospital
S. J. R.go M.D.
Section of C togenetics Department of Clinical Pathology, Royal Melbourne Hospital Melbourne, Australia

*Recipient of grant-in-aid G 438 from the National Heart Foundation of Australia.

REFERENCES

1. Barlow, J. B., and Bosman, C. K.: Aneurysmal protrusion of the posterior leaflet of the mitral valve, AM HEART J 71: 166, 1966.
2. T ll, M. E., Campbell, R. W., and Zimmer, J. F.: Late systolic murmurs and mitral regurgitation, Am. J. Cardiol. 15: 719, 1965.
3. Criley, J. M., Lewis, K. B., Humphries, J. O., and Ross, R. S.: Prolapse of the mitral valve—clinical and cineangiographic findings, Brit. Heart J. 28: 488, 1966.
4. Linhart, J. W., and Taylor, W. J.: The late apical systolic murmur, Am. J. Cardiol. 18: 164, 1966.
5. Stannard, M., Sloman, J. G., Hare, W. S. C., and Goble, A. J.: Prolapse of the posterior leaflet of the mitral valve, Brit. M. J. 3: 71, 1967.
6. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., and Hungerford, D. A.: Chromosome preparations of leucocyte cultures from human peripheral blood, Exper. Cell Res. 20: 613, 1960.
7. Thompson, J. S., and Thompson, M. W.: Genetics in medicine, London, 1966, W. B. Saunders Company.

Book reviews

SURGERY FOR ACQ D MITR L VALVE DISEASE By F Henry Ellis J M D Ph D Philadelphia & London 1967 W B Saunders Compa y 299 pages Pric $17.00

This monograph summarizes ery l the present tat of mi t l l surgery There ar six other contributor t the l k all from the M Clinic There is brief hist ry of the development of such surgery f llowed by chapters on erned th anat m pathology d gnosis hemodynam literat ms selection of patient for surgery nesthesia, nd surgic l tech ique of alv replacement nd prostheses, pre and postoper tiv management, complic tions nd resul The book end w th hapter concerned h the f tur of mi t l alv surgery The book ll ritten prof sely and learly illust ted There is f irl mplet bibliogr phy at the end of each hapter The dat and disc ssions are ac ur tel presented by surgic l team that has made importa t ontributions t ardio- sc lar surgery over the pa t ear This is eu llent book nd t is highl recommended t ll ph ia and med al tudent interested this importa t subject

RHE M IC A D CHRONIC H AR DISEASE Edited by Charles I Bailey M D Philadelphia & T ronto, 1967 J B Lippincott Company 284 pages Pric $15 50

This is ather brief disc ssion of importa t subject based pon mposium held t the Plaz Hotel New York Cit on December 10 through 12 1965 A total of 38 ph sicians in the rdiovasc lar field ont buted t the m- posium and this mpendi m Some of the n- luded papers are fairly good hereas other are extremely brief and poor The reader ha the impress on that some of the ontributors made ery little effort t rite good paper Furthermore the reader ll find little new toda in the proceedings Those ho wish to find one source discussions of medical nd surgical aspects of rheumatic al disc se nd of ic hemic heart disease may find this book of lue Unfortunately the discussions ar not critic lly presented so that the less informed eaders may gather the impression that these aspect of car diology are now fairly well solved

TRANSACTIONS OF THE INTERNATIONAL CHEST AND HEART CONFERENCE April 4 t 7 1967 Eas bourne the Chest nd H art Association T vistock House North T vistock Square London WC1 1967 303 pages Price $7.00.

This is the proceedings of the International Chest nd Heart Conferenc held in London on April 4 t 7 1967 The onference consisted of 17 ser t ns oncerned w th arious aspects of pul- monary nd ardiac disease Among the subject discussed were the outlook for the next ten ars f ngal h persensitivity best nursing in the future prevention of t ber ulosis, ps cho- somatic problem ancer of the lungs oronary thrombosis nd hypertension ir pollution st oke illness nd other The papers are short nd ontai ery few illustrations Many paper presented t the conference are not included in these tra sactions bec se the manuscript ere not rece ed on time for public tion The presen- tat ons ncluded are extremely brief nd the ader ll learn ery little new from them unless he happens t be one who fa ls t read his medical journals regularly However those ho sh t follow the activities of the conferences ll find that this paperbound book summarizes the eighth meet ng ery ell

TRAITEMENT DES LESIONS VAL UL IRES AORTIQUES P R DES GREF ES HETE OPLASTIQUES. B Mau C rpentier Paris 1966 R. Foulon & Cie 141 pages

This is concise review of the immunologic hni- l, and surgical problems related to the se of homographs nd heterographs n the repair of aortic al disease l ma The use of hetero- graphs, of course offers considerable imm no- logic difficulties hich the authors discuss ery ell. Included is a good bibliography and pre- liminary clinical results. The reader will find no new principles in thi monograph. It ill provide some impressions of the opinion of the French method and concepts regarding aortic al surgery

American Heart Journal

March 1968 Volume 75 Number

Editorial

The natural history of cerebral vascular disease

David C Wallace M B (Syd) M R C P (Lond) M R A C I
Goulburn New South Wales Australia

Cerebral vascular disease is one of the three main causes of death in countries with a technologically advanced economy Only arteriosclerotic heart disease and malignant disease are greater killers. It is important therefore that the natural history of this disease should be delineated with the utmost accuracy It has received very little attention in this regard principally because until recent years no measures had been proposed which definitively aimed at preventing or improving the condition. The advent of such proposals has made it imperative to have a clear understanding of the epidemiology of the disorder in order to have a standard with which to compare.

A study of mortality statistics can reveal much about the incidence of the disease and the variation of this incidence in relation to geographical distribution and to other factors such as age sex, race historical period and so on to an extent where definitive statements regarding death rates can be made as in the papers of Stallones Yates and Campbell. There is a sevenfold variation in reported incidence ranging from the figure in Japan 208 6 per 100,000 population) through those of Australia (118 0) and the United States (100 4) to that of Mexico (35.3) Even within countries such as the United States there is more than a twofold variation from one region to another in age adjusted death rates.

Over the years, there has been an increase in the incidence of death from vascular lesions of the central nervous system but this is largely due to the increasing proportion of elderly people in the populations of these countries. However more detailed analysis has revealed significant variation within certain categories of cerebral vascular disease Yates'[4] British study of trends in cerebral vascular disease death rates showed that although little change in the age-adjusted rate had occurred over the period 1932 to 1961 when the rates were separated into those due to hemorrhage and those attributed to thrombosis and embolism the former declined while the latter increased and this change was also found in a study of these diseases seen at autopsy in three Manchester hospitals. This pattern is more in keeping with the parallel increase in deaths from ischemic heart disease over the same period which suggests a relation between the two There appears to be a seasonal swing in death rates from cerebral vascular disease with a summer low and a winter high

Morbidity studies and longitudinal population studies are more difficult to obtain and as a result there are fewer comprehensive reports covering this field ceptable results include those

investigations of Eisenberg and co-workers, the Framingham report of Kannel and associates, our own Australian study and a smaller Japanese study. The results of these reports are in broad agreement and some interesting facts emerge.

In summary, our findings from an investigation which we feel resulted in almost complete ascertainment showed that the crude incidence of all forms of cerebral vascular disease in an Australian provincial community was 3.3 per 1,000 per year and of first attacks 2.6 per 1,000 per year. The greatest numbers came from the age group of 70 to 79 years. In the group 60 years old and over the incidence was close to 2 per cent per year. It was slightly higher in men than in women. Although the disease as it is seen in the community is one of women rather than of men (seven women are affected for every five men). The discrepancy between rate of incidence and numbers affected is due to the higher proportion of women among these higher age groups.

The prognosis in cerebral vascular attack is depressing. About one person in three dies during his or her first attack. Of the survivors, about one person in three will have a recurrence within the next two years and recurrences are most common soon after an attack, half of such recurrences occur within the first six months. In recurrent attacks the mortality rate per attack remains about one in three among people affected but there is a small proportion who suffer multiple small attacks that are not fatal. Those who suffer at least one recurrent attack are much more likely to have further recurrences and two out of three of these will have recurrences within two years. This has led certain investigators to formulate a concept of active cerebral vascular disease. Interestingly many cases, perhaps a majority,[8] will have been in poor general health before their stroke while one third will have had definite premonitory signs of some sort and half of these have a stuttering type of onset.

Cerebral vascular disease is of course a generic name for a number of different entities and these occur in the community in very different proportions to those found among acute hospital records. The great bulk of cases are due to cerebral infarction—63 per cent in the Framingham survey and 64 per cent in our own. Cerebral hemorrhage when diagnosed by strict criteria or by autopsy examination is much less common: 4 per cent in the Framingham study and 16 per cent in ours. Subarachnoid hemorrhage and cerebral embolism are of approximately equal incidence and cause between one sixth and one twelfth of the cases.

It is interesting to compare the disease with the other main categories of arterial disease, coronary artery disease and peripheral vascular disease. This has been done most satisfactorily by the Framingham workers who were able to demonstrate a much higher concurrence of two or more of these categories of disease than might have occurred by chance, thus strongly suggesting a common underlying cause for these conditions.

One point that was noted in our own study was that many cases arose as the result of an embolus following a myocardial infarct. Reduction in thromboembolic phenomena following anticoagulant therapy in myocardial infarction which Richards has convincingly demonstrated might be regarded as a point in favor of this form of treatment following an infarct. Certainly a cerebral embolus can be a devastating accident complicating an otherwise successful recovery from myocardial infarction.

It is imperative to give apparent stroke cases the full medical attention and investigation they deserve. A negative attitude will lead to the misdiagnosis of potentially remediable conditions as a small proportion of apparent strokes are due to other causes such as cerebral tumor and subdural hematoma, while the question of an antecedent cardiac condition must always be considered.

The prospect of long term survival following an attack of cerebral vascular disease is not good. More than half the cases having an initial attack will be dead within two years, while among those with recurrent attacks two thirds will be dead within this period. Surprisingly, among the survivors the incidence of severe impairment is not great. The majority attain independence in the activities of daily living

a minority continue to need help of some sort, but are able to live at home little more than ten per cent require as much as three months in a hospital or nursing home, and only a small fraction need continued nursing care.[6] This recovery rate suggests that a hopeful attitude to rehabilitation is well warranted

We tend to regard as little short of barbaric some of the medical practices of the Napoleonic era. It is a sobering thought that observers a century and a half ahead may look upon our methods with similar incredulous superiority It is easy to be persuaded that a fundamentally harmful line of treatment is brilliantly successful unless one refers back to the natural history of disease, which it is therefore most important to have marked out in the greatest detail

REFERENCES

1 Stallones, R. A Epidemiology of cerebrovascular disease, J Chronic Dis. 18:859 1965
2. Yates, P A. A change in the pattern of cerebrovascular disease, Lancet 1:65, 1964
3 Campbell, M The main cause of increased death rate from diseases of the heart 1920 to 1959 Brit. M J 2 712 1963.
4 Eisenberg, H. Morrison, J T Sullivan, P and Foot F M Cerebrovascular accidents. Incidence and survival rates in defined population, Middlesex County Connecticut, J A. M. A. 189:883, 1964
5. Kannel, W B Dawber T R., Cohen, M E., and Macnamara, P M Vascular disease of the brain—epidemiologic aspects The Framingham study Am J P b. Health 55 1355 1965.
6. Wallace, D C. A study of the natural history of cerebral vascular disease, M J Australia 1:90 1967
7 Katsuki, S., Omae, T and Hirota, Y Epidemiological and clinicopathological studies on cerebrovascular disease, Kyush J M Sc. 15 127 1964.
8. Marshall, J and Shaw D A. The natural history of cerebral vascular disease, Brit M. J 1 1614 1959
9 Richards, R. L. A ticoagulants in acute myocardial infarction clinicopathological study Brit. M J 1:821 1962.

Clinical communications

Acute effects of oral ethacrynic acid upon total blood volume

Philip Samet, M.D.
William H. Bernstein, M.D.
Miami Beach, Fla.

Previous studies have demonstrated that both the red cell mass and plasma volume are increased in patients with congestive heart failure regardless of the etiology of the heart disease. Effective therapy results in a statistically significant decrease in both volumes. Intravenous digitalis and/or mercurial diuretic therapy (in compensated and decompensated cardiac disease) failed to alter either red cell mass or plasma volume by six hours after drug administration. The purpose of this report is to describe our corresponding experiences with orally administered ethacrynic acid.

Methods and materials

Red cell mass and plasma volume were determined by methods previously published. A total of 30 patients were given 200 mg. of ethacrynic acid orally. In 25 red cell mass and plasma volume determinations were repeated three hours after drug administration. In five patients, these parameters were re-evaluated two hours after the oral ethacrynic acid. The red cell mass and plasma volume values were statistically analyzed before and after administration of the drug in order to detect the effect of the diuretic.

The diagnoses in the 30 patients included rheumatic and congenital heart disease and cor pulmonale. Most subjects were receiving digitalis but were not in clinical heart failure at the time of the study. Many had, however, previously exhibited symptoms and signs of heart failure.

Results

The control and postethacrynic acid data are shown in Table I. In the 3 hour study, the control plasma volume was 2,578 ml.; the experimental postethacrynic acid level was 2,282 ($P = 0.001$). The corresponding red cell mass data are 1,737 and 1,649 ($P = 0.001$). The differences in the mean total blood volumes and body hematocrits are also significant at the $P = 0.001$ level (Table I). In the 2 hour study, the difference in the body hematocrit is significant only at the $P = 0.05$ level; the red cell mass, plasma volume, and total blood volume all differ (at the $P = 0.001$ level) from the control level after oral administration of ethacrynic acid.

Discussion

The therapeutic value of ethacrynic acid in the treatment of acute pulmonary edema has been stressed of late. The

From the Section of Cardiology, Department of Medicine, Mount Sinai Hospital, Miami Beach, and the University of Miami School of Medicine, Coral Gables, Fla.
Supported by research grants from the National Heart Institute HE-09783-02 and Merck, Sharpe and Dohme.
Received for publication Feb. 16, 196

Table I. Blood volume after ethacrynic acid

Name	PV		RCM		TBV		Body HCT	
	C	*E*	*C*	*E*	*C*	*E*	*C*	*E*
Study I 3 hours								
D L.	2 744	2 233	2 787	2 924	5 531	5 157	50 3	56 6
C. \	2 720	2 609	1 387	1 394	4 107	4 003	33 7	34 8
\ G.	2 723	2 468	1 649	1 576	4 372	4 044	37 7	38 9
M E.	2 300	2 210	1 254	1 155	3 554	3 365	35 2	34 3
D D	2 534	2 272	1 834	1 643	4 368	3 915	42 0	42 0
E. C.	3 018	2 800	1 910	1 840	4 928	4 640	38 8	39 7
E. L.	2 397	2 298	1 719	1 677	4 116	3 975	41 8	42 2
H. F	2 278	2 077	1 628	1 542	3 906	3 619	41 7	42 6
M F	2 377	1 795	1 412	1 163	3 789	2 958	37 3	39 3
B H.	2 785	2 521	1 684	1 643	4 469	4 164	37 6	39 4
H L.	2 745	2 304	2 078	1 935	4 823	4 239	43 1	45 6
D L	3 179	2 774	2 445	2 296	5 624	5 070	43 5	45 2
M C	3 096	2 888	1 840	1 602	4 936	4 490	37 3	35 7
M R	2 293	2 027	1 819	1 648	4 112	3 675	44 2	44 8
C. D	2 003	1 711	1 076	993	3 079	2 704	34 9	36 7
\ T	2 970	2 750	1 978	1 862	4 948	4 612	40 0	40 4
\ \	2 379	1 931	2 199	2 131	4 478	4 062	49 1	52 5
\ C.	2 462	2 064	1 223	1 163	3 685	3 227	33 2	36 0
S. W	3 468	3 258	2 978	2 952	6 446	6 210	46 2	47 5
J B	1 944	1 639	1 421	1 350	3 365	2 989	42 2	45 2
D T	2 315	2 043	1 676	1 526	3 991	3 569	42 0	42 8
P R.	3 222	2 807	1 886	1 814	5 108	4 621	36 9	39 3
D K.	2 192	1 833	1 307	1 220	3 499	3 053	37 4	40 0
\. L	2 172	1 866	1 276	1 236	3 448	3 102	37 0	39 8
M C.	2 143	1 878	964	951	3 107	2 829	31 0	33 6
Average	2 578	2 282	1 737	1 649	4 312	3 932	39 8	41 4
Study II 2 hours								
N. M	2 171	2 041	1 912	1 804	4 083	3 845	46 8	46 9
G. W	3 182	2 734	1 780	1 657	4 962	4 391	35 9	37 7
H. R.	2 290	2 061	2 248	2 118	4 538	4 179	49 5	50 7
G. L.	1 942	1 625	1 006	930	2 948	2 555	34 1	36 4
\ F	1 823	1 597	1 376	1 315	3 199	2 912	43 0	45 2
Average	2 282	2 012	1 644	1 565	3 946	3 576	41 9	43 4

C, control. E, experimental.

rapid onset of a diuretic effect after oral or intravenous administration is in all probability the basic mechanism underlying the effect in pulmonary edema. A secondary result may be a decrease in total blood volume or true pulmonary blood volume. The effect of ethacrynic acid administration upon the latter parameter is now under study in our laboratory and will be reported at a later date. The data obtained in the present study demonstrate that there is indeed a significant decrease in plasma volume at both two and three hours after oral ethacrynic acid. The decrease in red cell mass is of smaller magnitude and is in large part due to the blood withdrawn during the two red cell mass and plasma volume determinations. An earlier study has demonstrated that phlebotomy in patients in congestive heart failure does not significantly alter plasma volume. The plasma volume removed during the phlebotomy is largely restored to the circulating blood volume by hemodilution within one hour after phlebotomy.[4] In

contrast red cell mass is not acutely restored after phlebotomy Earlier studies from this laboratory have shown that neither digitalis nor mercurial therapy acutely alters plasma volume Despite the probable partial replenishment of plasma volume from the extracellular volume during ethacrynic acid diuresis, a significant 300 ml decrease in plasma volume is evident by 2 to 3 hours after oral drug administration Ethacrynic acid is therefore more effective than phlebotomy in producing a persistent (not transient) decrease in plasma volume Similar data on the acute effects of ethacrynic acid on blood volume are not available in the literature although Nash and associates[12] have reported subacute effects of this drug One further point is worthy of stress. The red cell mass decrements noted after ethacrynic acid cannot of course be attributed to the diuretic effects of ethacrynic acid approximately 80 ml of red cells are removed for various purposes during the course of the two red cell studies performed in this investigation thereby accounting for the largest portion of the observed decrease in red cell mass.

The observations reported in this study provide a firm basis for the intravenous or oral use of ethacrynic acid in the therapy of patients with varying degrees of pulmonary edema

Summary

The acute effects of oral ethacrynic acid administration upon red cell mass and plasma volume are reported in 30 patients. A significant decrease in plasma volume has been observed and is in all probability secondary to the profound diuretic effect of the drug unlike the transient effect of phlebotomy which is largely gone by one hour The effect of ethacrynic acid in lowering the plasma volume persists for at least 2 to 3 hours. The therapeutic implications for the patient with pulmonary edema are readily evident.

REFERENCES

1 Samet, P Fritts, H. W J Fishman A. P nd Cournand A. The blood volume in heart disease Medicine 36:211 1957
2 Schreiber S. S., Ba man, A Y low R. S and Berson, S. A Blood volume alteration I congestive heart failure, J Clin. I vest. 33:578, 1954
3. Samet P and Bernstein, W H: U published observations.
4 Samet P Bernstei W H and Boucek, R. Effect of the pplication of venous tourniquets on blood vol me Am J Cardiol. 8:369 1961
5 Rosenberg, B Dobkin, G., nd R bin R. The I travenous use of ethacrynic acid in the man agement of acut pulmonary edema, Am HEART J 70:333, 1965
6. Fine S. L., nd Levy R. I Ethacrynic acid i acute pulmonary edema, New England J Med. 273:583, 1965.
7 Led ngham, J G. G. Ethacry ic acid parenterally in the treatment and prevention of pulmonary edema, Lancet 1 952, 1964
8. Zatuch k J The diuretic effects of travenously administered ethacry ic acid Am. J M Sc 252 162, 1966.
9 Milnor W R Jose A. D nd McGaff C. J Pulmonary vascular volume resistance and compliance in man, Circulation 22:130, 1960.
10. Dock, D S., Kraus, W L., McGuir L. B Hyland, J W H ynes, F W and Dexter L. The pulmonary blood volume in man, J Clin. Invest. 40:317 1961
11 Samet P and Bernstein, W H. Am J M Sc (in press)
12. Nash, H. L Fitz, A. E., Wilson, W R., Kirkendall, W M., and Kioschos, J M Cardiorenal hemodynamic effects of ethacrynic acid, Am H ART J 71 153 1966.

Sponge electrodes for recording the vectorcardiogram of children

A. Calhoun Witham, M.D.
Augusta, Ga.

Frank's design of the first vectorcardiographic lead system combining acceptable orthogonality and practicality stimulated new interest in quantitative vectorcardiography. The resistances employed in order to approach orthogonality with the Frank circuit, however, were calculated from studies on the adult torso and are not necessarily corrective in children. An admitted weakness is the assumption that one can consistently place the belt of chest electrodes in the same horizontal plane as the cardiac dipole. Some investigators have utilized the fifth and others the fourth intercostal space.[3] Another disturbing feature is the sensitivity of the loop in the horizontal plane to minor variations in the position of the C electrode.

It seems doubtful that Frank's arrangement represents a final choice of systems. One was sought which retained its practicality but circumvented the above objections. The system proposed by Helm in which two large gauze or sponge squares, saturated with saline, are used as electrodes in the X and Z leads seemed to fit these requirements. The conductive squares apparently function as do banks of electrodes covering the same area.[4] Similar grid electrodes are apparently less sensitive to dipole position than the Frank band. Another appealing feature especially for its application to children is that equal lead vectors for X, Y, and Z are not dependent on input resistances but on integration of surface potentials from critically large areas on anterior and lateral chest walls.

Sponge electrodes have gradually displaced cube and Frank leads in our laboratory. They seem particularly adaptable for children since sponges of appropriate size can be cut quickly. The present study reports diagnostically useful data from a normal series. In addition, normal variability is compared with that reported for the Frank system. Some general statements concerning the influence of age and sex on the vectorcardiogram (VCG) of children seem justified and differences from the adult VCG are noted. Finally, special consideration is given to the terminal vector forces because of their importance in the diagnosis of right ventricular disease.

Methods

Patients. A total of 79 children ... to 16 years of age and judged to have normal cardiovascular systems on the basis of history, physical examination, chest x-ray, and hemogram were studied. Standard electrocardiograms (ECG's) were used to exclude major bundle branch block. Six,

From the Department of Medicine, Division of Cardiology, Eugene Talmadge Memorial Hospital, and Medical College of Georgia, Augusta, Ga.

Received for publication March 1, 1962.

however with normal QRS duration showed RSr′ complexes in V_1 and are analyzed separately There were 42 boys and only three were Negroes. About 50 per cent were children of faculty and housestaff 25 per cent were from a state institution for the mentally retarded and the rest were principally from the pediatric surgical service Fig 1 reveals sex and age distribution and identifies those with the ECG patterns of RSr′ in V_1 and with loops of Fig 8 configuration in the horizontal plane

Recording measurement and analysis of data Loops in the frontal (fp) horizontal (hp) sagittal plane (sp) and scalar orthogonal leads were recorded from unsedated patients in the recumbent position Two square porous plastic sponges, ¼ inch thick, were saturated with saline and used as positive electrodes for the X and Z leads respectively Their size varied with that of the child and was tailored to fulfill Helms original specification for the largest area feasible on anterior and left lateral chest For Lead X the sponge was cut to cover a square area bounded by left mid clavicular and posterior axillary lines and centered at the level where the fifth inter costal space intersected the parasternal lines. The square for Lead Z was identically centered and bounded laterally by the anterior edge of the X sponge (but not touching it) and a symmetrically identical vertical line on the right The negative electrodes were single pediatric limb electrodes positioned in the right axilla (X) and back (Z) as recommended by Helm The Y lead consisted of electrodes in the right supraclavicular fossa or on the fore

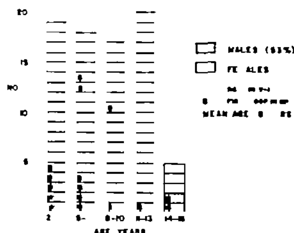


Fig 1 Age and sex distribution of 79 patients. Those whose ECG and VCG are given special attention in the text are indicated

Table I Quantitative data on normal QRS loops ages 2 to 15 years —Helm system

	Q		20 msec	
Angles (degrees)				
FP	190 ± 56	(20 275)*	81 ± 70	(10–320)*
HP	112 ± 20	(60–135)*	71 ± 20	(30–105)
SP	353 ± 27	(305–55)	24 ± 20	(345–65)
Voltage (mv)				
FP	0 24 ± 0 14	(0–0 50)	0 43 ± 0 31	(0 1 1 3)*
HP	0 39 ± 0 17	(0 1–0 9)*	0 65 ± 0 25	(0 2 1 2)*
SP	0 39 ± 0 18	(0 1–0 8)*	0 71 ± 0 27	(0 3–1 2)*
Spatial	0 42 ± 0 19	(0 1–0 9)*	0 75 ± 0 30	(0 3 1 4)
Timing (msec)	11 ± 3	(7 16)	——	
	Anterior duration = 35 ± 7 (25–52)*			
	Initial superior duration = 11 ± 8 (0–24)*			
Voltage orthogonal leads (mv)	X R = 1 17 ± 0 33	(0 6–2 1)		
	Y R = 1 47 ± 0 43	(0 8 2 5)		
	Z R = 0 64 ± 0 27	(0 2 1 3)*		
				R + S =

*Non-Gaussian distribution.
Ranges, 97 per cent of observations.

head and the left leg Records were photographed on an Electronics for Medicine recorder Since only the QRS loop was to be studied in detail P and T loops were electronically deleted when necessary to clarify initial and terminal forces. The right sagittal project on was used and loop interruptions were at 4 msec intervals.

The selection of points to be measured was based on the observations of Peñaloza and Tranchesi and Sod Pallares and associates that three vectors usually describe the normal loop We have defined these as follows. The R vector is identified by the most leftward point. Q and S are identified as major changes in direction (at least 75 degrees in two or more planes) Q is the first such shift after the beginning of the loop and S is the first past the R point In addition a fourth vector M the max mum vector was measured in each plane A fifth vector 20 msec. after the onset of the QRS loop was also quantitated Finally n 16 per cent of the loops, a distinct final change in spatial direction past the S point was identified designated the S vector nd its characteristics recorded because of its mportance n loops reflecting right ventricular hypertrophy and bundle branch block This general scheme has been used before

The angles of vectors in each plane were recorded according to the suggestion of Helm[12] Spatial voltages were calculated by a nomogram solving the Pythagorean equation The time of appearance of Q R and S vectors, the duration of initial superior and anterior forces of the entire QRS loop and of the S loop (from the S point to the beginning of the T loop) were recorded Finally the voltage of the major deflections of the scalar Leads X Y and Z and the voltage sum of R and S were noted Thus, 48 measurements were made for each complete VCG Computer programs were designed to yield mean, standard deviation standard error test for normality and coefficient of correlation of each variable with every other Correlation coefficients between age and the 48 vector measurements were also obtained The ranges quoted include 97 per cent of observations obtained by eliminating the single highest and lowest measurement and should approximate M ± 2 SD when frequency-distribution is normal. T tests were done to ident fy significant differences between measurements in boys and girls and between these same parameters in a group of 133 young adults previously studied.[11] Variab l ty of measurements of angles and voltages was com-

R		S		M	
31 ± 10	(30-70)	161 ± 79	(20-283)	54 ± 11	(30-75
4 ± 1	(335-45	258 ± 22	(200-295)	6 ± 41	(270-60)
83 ± 34	(60-110	377 ± 30	(130-230)	94 ± 28	55-200
1 87 ± 0 39	(1 1 2 7	0 36 ± 0 23	(0-0 8)	1 9 ± 0 40	(1 1 7
1 21 ± 0 31	0 8 1 9	0 66 ± 0 30	(0 1 1 5)	1 25 ± 0 28	(0 9-1 9)*
1 46 ± 0 41	(0 7 2 4)	0 72 ± 0 33	(0 -1 6)	1 90 ± 0 4	(0 9-2 5
1 9 ± 0 40	(1 2	0 75 ± 0 33	(0 2 1 7)*		
34 4	(26 44	53 ± 8	(40-72)	——	
		Total QRS duration ± 74 ± 8 (58 85			
		S loop duration ± 22 ± 6 (10-3			
		S ± 0 18 ± 0 18	(0-0 7)		
		S ± 0 37 ± 0 19	(0-0 6)*		
		S ± 0 65 ± 0 31	(0 -1 5)*		
1 46 0 46	(1 1 81				

Table II *Statistical basis for correlations mentioned in text*

			$p <$
I fluenc f frontal pla u			
R angle I P vs	M angle in FP	0 87	0 001
	Q ngle i FP	0 37	0 01
	Du tion tial superior forces	0 41	0 001
	Voltage R HI	−0 61	0 001
	Voltage R i V	−0 50	0 001
	Voltage R + S	−0 37	0 001
I fl en f ge			
Age y ars vs	Duration total QRS	0 38	0 001
	Dur tion anterior forces	0 26	0 05
	Time of R ector	0 29	0 05
	Volt ge Q HP	−0 29	0 05
	Volt ge Q in SP	−0 35	0 01
	V ltage Q spatial	−0 28	0 05
	Voltage 20 msec I III	−0 25	0 05
	V ltage R Z	−0 23	0 05

When = 0 23 p < 0 05
= 0 30 p < 0 01
= 0 38 p < 0 001

pared to that reported for children studied by the Frank system and with similar measurements in young adults studied by the Helm technique.[11] A two-tailed test of variance (F) was used for comparisons of angles and coefficient of variation (CV) for voltage

Results

Table I presents the means, standard deviations, and ranges for the 48 variables. Table II contains the correlation coefficients and confidence limits for correlations alluded to in the text. Table III summarizes direction of inscription in the three planes. Table IV reports significant results of t testing the measurements of men against those of women and of the children against those of a group of normal young adults. Tables V and VI compare the variability of these measurements with that of those from a similar series of children studied by Frank's system[4] and with that of measurements from a group of young adults studied by Helm's system. Table VII describes quantitatively the terminal forces in the loops of six patients whose ECG's revealed an RSr′ configuration in V_1 Table VIII tabulates the characteristics of the S vector in the 13 loops in which it could be identified.

Table III *Rotation of QRS loop (percentage)*

	CW	CCW	Fig 8
Front			
Q20	30	70	—
QRS	21	18	61
Horiz.			
Q20	0	100	—
QRS	0	78	22
Sag			
Q20	100	0	—
QRS	95	0	5

*Data from 73 children Patients with RSr′ in V excluded. Fig 8 defined as any complete reversal of direction no matter how brief Q20 segment is the first 24 msec of the efferent limb

Fig 2 compares mean loops obtained from children with the Frank[4] and Helm systems. Fig 3 superimposes average loops obtained with sponge electrodes from children and young adults. Fig 4 plots individual angles and voltages of the S vector Fig 5 illustrates the problem of differentiating normal from right ventricular disease by VCC when the ECG reveals an RSr′ pattern in V

Table IV. Significant differences (t test) by sex and age

A Between male and female children

Variable	Males (Mean ± S.E.)	Females (Mean ± S.E.)	t	p <
Angle R in SP	81.8 ± 2.49	89.2 ± 2.02	−2.21	0.05
Voltage R in FP	1.77 ± 0.059	1.99 ± 0.066	−2.44	0.05
Voltage R in SP	1.37 ± 0.065	1.57 ± 0.068	−2.100	0.05
Voltage R, spatial	1.83 ± 0.057	2.03 ± 0.073	−2.14[illegible]	0.05
Voltage S in Lead X	0.23 ± 0.033	0.12 ± 0.021	2.655	0.01

B Between children and adults

Voltage variables (mv)	Adults (Mean ± S.E.)	Children (Mean ± S.E.)	t	p <
Q in FP	0.14 ± 0.008	0.[illegible]4 ± 0.016	−5.[illegible]8	0.001
20 msec in FP	0.24 ± 0.014	0.43 ± 0.036	−5.92	0.001
R in FP	1.62 ± 0.038	1.87 ± 0.043	−3.99	0.001
M in FP	1.67 ± 0.038	1.93 ± 0.046	−3.90	0.001
Q in HP	0.20 ± 0.009	0.39 ± 0.070	−9.42	0.001
20 msec in HP	0.34 ± 0.013	0.65 ± 0.029	−10.74	0.001
R in HP	1.07 ± 0.034	1.21 ± 0.036	−2.7	0.01
S in HP	0.53 ± 0.032	0.66 ± 0.034	−3.32	0.01
M in HP	1.10 ± 0.032	1.25 ± 0.033	−3.99	0.01
Q in SP	0.21 ± 0.010	0.39 ± 0.0[illegible]1	−8.68	0.001
20 msec in SP	0.35 ± 0.013	0.71 ± 0.031	−12.07	0.001
R in SP	1.[illegible]4 ± 0.035	1.46 ± 0.[illegible]48	−5.80	0.001
S in SP	0.56 ± 0.024	0.72 ± 0.039	−3.65	0.001
M in SP	1.34 ± 0.034	1.59 ± 0.049	−4.28	0.001
Q—spatial	0.23 ± 0.011	0.42 ± 0.021	−9.24	0.001
20 msec—spatial	0.34 ± 0.014	0.75 ± 0.034	−11.61	0.001
R—spatial	1.65 ± 0.040	1.92 ± 0.046	−4.16	0.001
S—spatial	0.60 ± 0.025	0.75 ± 0.039	−3.31	0.001

Discussion

Relation of frontal plane axis to other measurements. The axis of the loop in the fp as defined by the position of the R and M vector must be considered in deciding if certain measurements are normal. As R axes become more vertical the angle between Q and R vectors remains relatively constant, so that Q tends to be directed superiorly. In the more vertical loops, one therefore expects the duration of the initial superior forces to be longer. The rotation of the loop in the fp is therefore generally clockwise with vertical loops and counterclockwise with horizontal ones. As the R or M vector shifts vertically leftward forces (R) diminish. The sum R + S, an index of left ventricular hypertrophy,[8] decreases since the loop is inscribed mainly along the vertical (Y) axis. Perhaps a better index would include a measurement (e.g. R) incorporating this possibility. The confidence limits for the above statement are recorded in Table II.

Comparison with the Frank VCG. Langner[4] made comparisons of the Helm and Frank lead vectors for X, Y and Z and found that although X was similar, the Helm system yielded slightly higher values for Z and about 30 per cent higher for Y. This is compatible with the generally higher voltages observed in the Helm data (Fig. 2). The differences are striking only for vectors which contain a large Y component (fp and sp). M vectors are somewhat more posterior in the Frank

Table V. Variability of measurements: children (Frank vs. Helm)

Variable	Angles				Voltage	
	SD_F	SD_H	F	$p <$	CV_F	CV_H
10 msec.—Q						
FP	—	56		—	55	58
HP	22	20	1.21	NS	52	44
SP	20	27	1.83	0.01	47	46
20 msec.						
FP		70	—		67	72
HP	23	20	1.33	NS	40	38
SP	21	20	1.10	NS	41	38
30 msec.—R						
FP	16	10	2.55	0.01	39	21
HP	26	16	2.64	0.01	40	26
SP	24	14	2.89	0.01	44	28
40 msec.—R						
HP	34	16	4.39	0.01	34	26
SP	26	14	3.45	0.01	40	28
M vector						
FP	10	11	1.21	NS	32	21
HP	43	41	1.10	NS	40	22
SP	39	28	1.95	0.01	44	26
50 msec.—S						
FP	—	79	—	—	—	—
HP	15	22	2.15	0.01	50	45
SP	19	30	2.50	0.01	47	46

SD_F, SD_H, standard deviation, Frank and Helm respectively. F, variance, larger SD²/smaller SD². CV_F, CV_H, coefficient of variation (SD/Mean × 100), Frank and Helm respectively. NS, not significant, p > 0.05.

loops. In adults, also Pipberger and associates[4] observed that the posterior component of Z was dominant with the Frank recordings, whereas anterior and posterior deflections are nearly equal with the Helm.[4] There is remarkable similarity of the angles of early and late vectors in the two systems.

Influence of age and sex. Within this series, there was surprisingly little change related to age. The best correlation was with total QRS duration, a fact previously noted. Several other time measurements, probably a reflection of the above, were also related. The voltage of anteriorly directed vectors (Q, 20 msec.) seems to decline with age, but the statistical significance is minimal (Table II).

When this group is compared to the series of young adults, however, voltages are consistently higher in the children (Table IV, Fig. 3). The difference is greatest for the anterior vectors, so that a little more of the loop tends to be inscribed in the anterior hemisphere. The suggestion of decreasing voltages with age, particularly for anterior vectors, therefore, is confirmed when the age range is extended by this comparison. Hugenholtz, using the Frank system, also noted larger voltages in children for early and late vectors, but in our study mid loop vectors were also significantly larger. There was striking similarity of angles for the five vectors measured in the two age groups (Fig. 3).

In adults, voltages are significantly higher in males.[1,21] In children, however, this trend is absent and even the opposite is suggested (Table IV). Due to the minimal influence of age and sex on the VCG between ages 2 and 15, it seems unlikely that further stratification of normal ranges would have practical value.

Variability of measurements: comparison with the Frank system and with adults. In general, tests which give the smallest scatter of normal values are likely to be the most sensitive in detecting the ab-

Table VI Variability of measurements adults vs children (Helm system)

Variable	Angles				Voltage	
	SD	*SD*	*F*	*p* <	*CV*	*CV*
Q						
FP	69	56	1.51	NS	64	58
HP	26	20	1.69	0.05	55	44
SP	32	27	1.43	NS	57	46
Spatial	—	—	—	—	59	45
20 msec.						
FP	85	70	1.48	NS	72	71
HP	34	20	2.90	0.01	38	44
SP	37	20	3.43	0.01	38	43
Spatial	—	—	—	—	40	45
R						
FP	14	10	1.96	0.01	21	25
HP	16	16	1.00	NS	26	36
SP	20	14	2.02	0.01	28	33
Spatial	—	—	—	—	21	29
S						
FP	74	79	1.14	NS	64	75
HP	24	22	1.19	NS	45	49
SP	33	30	1.21	NS	46	50
Spatial	—	—	—	—	44	48
M						
FP	21	11	3.63	0.01	21	24
HP	57	41	1.93	0.01	22	36
SP	30	28	1.15	NS	26	31

SDa, SDc, standard deviation, adults and children respectively; F, variance, larger SD²/smaller SD²; CVa, CVc, coefficient of variation, adult and children respectively; NS, not significant, [illegible]

normal. It was considered of interest, therefore, to compare the variability of these measurements with those reported by Hugenholtz[3] for the Frank system. Timed consecutive vectors were used by this author to quantitate the VCG. Since the location of the mean vector is of no interest in this regard, a two tailed test of variance was deemed satisfactory for comparing distribution of angles as it involves only standard deviation (variance ratio or F = larger SD²/smaller SD²). Coefficient of variation, however, seemed more appropriate to compare voltage distribution since the means are distinctly higher for the Helm system (Fig. 2) and standard deviation would therefore be expected to be higher also. CV, of course, corrects for mean values of different orders of magnitudes (CV = $\frac{SD}{M} \times 100$).

The results (Table V) indicate that when the angles of similarly defined vectors are compared (20 msec. M) distribution is relatively similar. The R vector Helm however appears to show considerably less scatter than either the 30 msec. Frank, M vector Frank, or 40 msec. Frank. This superiority could be due either to the choice of the R point or to the poor performance of the Frank Z lead as suggested by Hugenholtz. Comparisons do suggest that vectors defined morphologically (Q, R, S) are somewhat more stable than those defined at fixed time intervals.[11] The coefficients of variation for voltage are also consistently lower for the Helm R and M vectors than for their Frank counterparts. On the other hand, variance of the Helm S point is higher than that of the Frank 50 msec. vector. Nonetheless, the 50 msec. vector in practice has not been as useful in quantitating right ventricular overload as maximum vector to the right[7,14]—which is nearly always the S or S vector

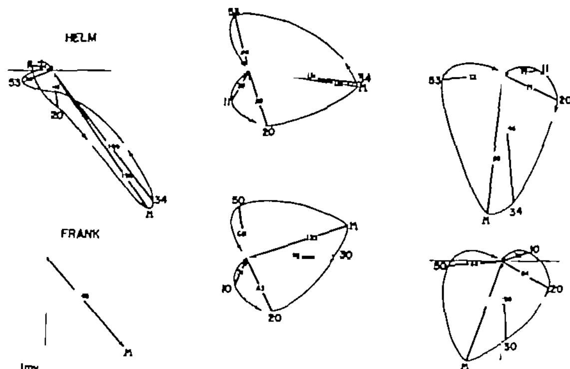


Fig. 2. A ag loops prepared from data obtained ith sponge electrodes nd by H genboltz[4] ith the Fra k stem Frontal, horizontal and sagittal planes are represented in order from left t right The figures outside th loops reflect the erage t me (msec) for the ppearance of Q R S or 20 msec ectors i the top set and of t med onset tn ector the low The sket hed loops are accur t only t these poi ts. In both the figures interrupting the ector lines reflect verage oltage (mv) and M refers to the max mum ector in each plane Frank data report only M in the frontal plane The Helm loops ha more anterior orient tion and larger oltages for ectors th large Y component.

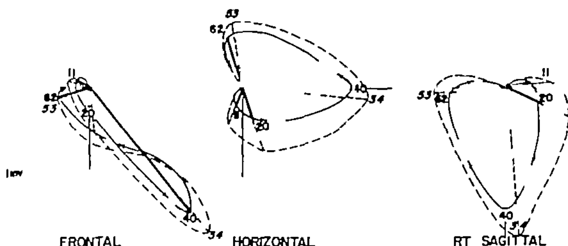


Fig. 3. A erage loops prepared from data obtained w th sponge electrodes i children (i terrupted lines) nd a group of young adults (solid line) Frontal, horizontal nd sagittal planes are presented from left to right Q 20 msec R and S vectors are draw for each and the loops sketched in The average time of their appear nce (msec) is denoted by the numbers and is similar in both groups here only one is present. T ble IV contains statistical comparison of voltages. The angles are independent of age.

Table VII. Characteristics of terminal forces in loops from patients with RSr' in V

	Mean (range)
HP	
Duration of secondary loop (msec.)	25 (7 35)
S angle (degrees)	206 (165–230)
S' ngle (degrees)	235 (215–255)
S oltage (mv)	0 43 (0 3–0 7 mv)
S' voltage (mv)	0 36 (0 2–0 5 mv)
Ratio S/R voltage	0 33 (0 17–0 45)
FP	
S angle (degrees)	186 (120–225)
S' angle (degrees)	240 (215–265)
S voltage (mv)	0 41 (0 2–0 6 mv)
S' oltage (m)	0 40 (0 2–0 6 mv)
Width/length ratio	0 23 (0 12–0 40)
Rotation 2CW	2 CCW 2 Fig 8

The results by this method of assessment suggest that the over-all performance of the Helm loops in children as analyzed is as satisfactory and in some respects superior to that of Frank loops analyzed by timed consecutive vectors.

Since the ECG of childhood is generally thought to be more variable than that of adults, this was investigated for the VCG As voltages are distinctly higher in children CV was again used to compare voltage distributions. Variance ratio (F) was used for comparison of angles (Table VI) With the exception of the Q vector voltage measurements are indeed more stable in adults. In contrast there appears to be less variability in the angles of 20 msec. R, and M vectors of children. In summary then, these tests suggest that the

Table VIII. Description of S' vector

Plane	*Angle (degrees) mean (range)*	*Angle with S* mean (range)*	*Voltage (MV) mean (range)*	*Voltage S'/S mean (range)*
FP	259 (230–300)	80 (−70 + 230)	0 30 (0 10–0 45)	1 56 (0 13–3 40)
HP	256 (205–305)	2 (−15 + 20)	0 45 (0 10–0 70)	0 81 (0 36–2 00)
SP	216 (190–250)	49 (10–115)	0 46 (0 20–0 75)	0 89 (0 13–2 00)
Spatial			0 56 (0 29–0 75)	1 15 (0 32 3 00)

*Angle with S = Angle of S' − Angle of S

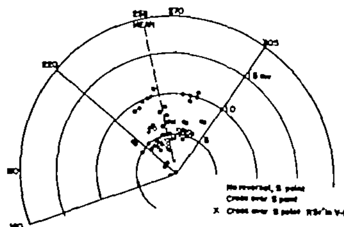


Fig 4 Voltage-angle plot of normal S vectors in the horizontal plane Degrees are indicated outside the circle and centripetal oltage scale is presented along the line indica ing 305° Points representing Fig 8 loops nd RSr complexes in V tend toward the right.

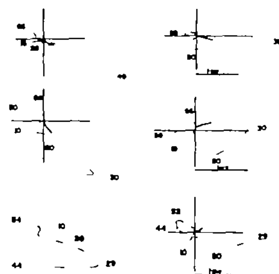


Fig 5 Frontal (left) and horizontal (right) loops three patients exhibiting an RSr' complex in Lead V. Time interruptions are at 4 msec intervals The figures refer to the appearance times of Q 20 msec R and S vectors and the bottom two examples also of an S' vector The top set is typically normal although the S vector is unusually far to the right (hp) It is however of small magnitude both absolutely and in relation to the R vector The loop in the fp is narrow rotation generally counterclockwise, the S vector is above 180° and of less than 0 5 mv The bottom group are from a child of the same age (5 years) with a small secondary atrial septal defect and has numerous abnormal features In the hp the cross-over is anterior to the null point and S and S' vectors have higher voltage relative to R. The most distinct difference however is in the fp The S vector is characteristically in the right lower quadrant and exceeds 1 mv causing dominant clockwise rotation with more open loop (greater width-length ratio) The middle example is the only normal Fig 8 loop in the hp which exhibited cross-over anterior to the null point Although the hp has features definitely suggesting right ventricular overload, the fp loop has only normal characteristics—narrow counterclockwise and with superior S and S' vectors of normal magnitude.

VCGs of children have generally more variable voltages but somewhat less variable angular measurements

RSr' in V₁ and the Fig 8 loop in the horizontal plane All six patients with RSr' pattern in V had Fig 8 loop configurations in the hp with a secondary loop formed about the S point but one was inconstant. Frequently the loops were indistinguishable from others without the ECG pattern Nevertheless, S vectors were generally oriented more to the right than usual (Fig 4) They may simply form one end of the frequency distribution curve of S position in the hp and with this orientation cross-over is more likely as the loop closes. Both the ECG pattern and the Fig 8 hp loop are more frequent at the earlier ages (Fig 1) and may represent incomplete evolution of the more anteriorly directed S vector of infancy The two explanations are of course not mutually exclusive.

Of the 14 Fig 8 loops in the hp but without RSr' in V₁ 12 had cross-overs involving only the S point (Table III) In one a small secondary loop was present only at the R point and in another crossing occurred at both the R and S points. The crossings involving the S loop were posterior to the null point as reported for the Frank system

The S' vector The terminal portion of the loop shows the earliest alterations in right ventricular disease and its normal variations therefore deserve the closest scrutiny Significant variations in detail may occasionally escape mensuration unless more than one late vector is measured The concept of an S' vector fills this need. It is defined as a *second* major change in direction past the R point. The arbitrary limits for its identification are that it must occur at least 8 msec. after the S vector and that it be reflected in two or more planes as a change in direction of at least 75 degrees. It was noted in 3 of 6 of the RSr loops discussed above (Fig 5) and in 10 of the 73 other cases (16 per cent of 79 cases) Its angles, voltages, and relationship to its accompanying S vector are recorded in Table VIII The RSr' loops are not included Its general characteristics can be deduced from the table It is always superior and generally above the S vector It is nearly always obvious in fp and sp but because it is oriented posteriorly on the closing limb may not be distinct in the hp. Its voltage may be smaller or greater than the S vector but is of the same order of magnitude. In patients with right ventricular disease, it is usually present and its quantitative features perceptibly altered

Conclusions

A total of 79 normal children from 2 to 15 years of age have been studied by the

VCG lead system proposed by Helm. Voltages and angles for six vectors have been recorded and certain comparisons made. The principal differences from loops recorded by the Frank system are attributed to the higher voltages of the Y axis and to a relatively more prominent anterior component of the Z lead. Within this age group there was a barely detectable decrease in voltage with age but this tendency became highly significant when comparison was made with a similarly studied group of young adults. Vector angles, however were independent of age. Unlike adults, males did not have significantly higher voltages. Variability of the measurements of the selected vectors were compared with those reported for the Frank system. Performance was comparable except that the measurements of mid loop vectors reported for the Frank system were more variable. When compared to young adults, also studied by the Helm system, voltage measurements of children were generally more variable but some angles less so. Considerable attention is given to variations in the terminal portion of the loop and quantitative aspects of the VCG in patients with the ECG pattern of RSr' in V are recorded. Finally a late vector S' found in 16 per cent of records, is described.

REFERENCES

1. McCall, B. W., Wallace, A. G., and Estes, E. H.: Characteristics of the normal vectorcardiogram recorded with the Frank lead system, Am. J. Cardiol. 10:514, 1962.
2. Draper, H. W., Peffer, C. J., Stallman, F. W., Littman, D., and Pipberger, H. V.: The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system), Circulation 30:853, 1964.
3. Hugenholtz, P. G., and Liebman, J.: The orthogonal VCG in 100 normal children (Frank system) with some comparison data recorded by the cube system, Circulation 26:891, 1962.
4. Helm, R. A.: An accurate lead system for spatial vectorcardiography, Am. Heart J. 53:415, 1957.
5. Langner, P. H., Jr., Okada, R. H., Moore, S. R., and Fies, H. L.: Comparison of four orthogonal systems of vectorcardiography, Circulation 17:46, 1958.
6. Fischmann, E. J., and Elliot, B. J.: Experimental comparison of "parallel grid" leads with simple bipolar and the SVEC III, Frank, and McFee-Parungao systems. I. Sagittal leads, Am. Heart J. 6 : 792, 1964.
7. Fischmann, E. J.: Experimental comparison of "parallel grid" lead with simple bipolar and the SVEC III, Frank, and McFee-Parungao systems. II. Transverse and vertical leads, Am. Heart J. 6:627, 1965.
8. Brody, D. A., and Arzbaecher, R. C.: A comparative analysis of several corrected vectorcardiographic leads, Circulation 29:533, 1964.
9. Pedaloza, D., and Tranchesi, J.: The three main vectors of the ventricular activation process in the normal human heart. I. Its significance, Am. Heart J. 49:51, 1955.
10. Sodi-Pallares, D., Bisteni, A., Medrano, G. A., and Ayala, C.: Clinical cardiopulmonary physiology, ed. 2, New York, 1960, Grune & Stratton, Inc., p. 63.
11. Witham, A. C.: The vectorcardiogram recorded with sponge electrodes, Am. Heart J. 72:730, 1966.
12. Helm, R. A.: Vectorcardiographic notation, Circulation 13:581, 1956.
13. Steele, R. G. D., and Torrie, J. H.: Principles and procedures of statistics with special reference to the biological sciences, New York, 1960, McGraw-Hill Book Company, Inc., p. 82 (F) p. 20 (CV).
14. Yano, K., and Pipberger, H. V.: Correlation between radiologic heart size and orthogonal electrocardiograms in patients with left ventricular overload, Am. Heart J. 67:44, 1964.
15. Witham, A. C.: Quantitation of the vector cardiogram, Am. Heart J. 72:281, 1966.
16. Hugenholtz, P. G., and Gamboa, R.: Effect of chronically increased ventricular pressure on electrical forces of the heart: correlation between hemodynamic and vectorcardiographic data (Frank system) in 90 patients with aortic or pulmonary stenosis, Circulation 30:511, 1964.
17. Namm, E. P., and D'Arruz, I. A.: The vector cardiogram in normal children, Brit. Heart J. 26:689, 1964.

Cardiac function following mitral valve replacement

H Hultgren M.D
H Hubis M.D *
N Shumway M D ***
Palo Alto Calif

Wide application of prosthetic replacement surgery for severe valvular heart disease quickly followed the initial demonstration of the effectiveness of the caged ball valve prosthesis by Starr and his associates. The technical effectiveness of the Starr Edwards prosthesis and the continued excellent function up to five years after insertion have been demonstrated [1-4] Postoperative hemodynamic studies have indicated only small pressure gradients across the valve at rest with a moderate increase being observed during exercise Examination of cardiac function following mitral valve replacement reveals a striking decrease in left atrial and pulmonary artery pressure and an increase in cardiac output. [7] Residual abnormalities in pressure and cardiac output, especially during exercise persist however and the nature of these abnormalities remains to be elucidated It is the purpose of this study to examine cardiac function following mitral valve replacement with particular emphasis upon cardiac output and pulmonary vascular pressures at rest and during exercise.

Methods

A total of 27 patients were selected who had obtained an excellent result from mitral valve replacement. Studies were performed preoperatively and from 3 to 22 months postoperatively (mean 6.8 months) None of these patients had significant disease of the aortic or tricuspid valve. Valve replacement (Starr Edwards prosthesis) was performed in a manner which has been previously described [8] The postoperative course in all patients in this group was uncomplicated and none of them had any evidence of a regurgitant leak around the prosthesis. Prior to the postoperative study three patients with atrial fibrillation were electroverted to a stable sinus rhythm Nearly all patients were receiving digitalis at the time of the preoperative and postoperative studies.

Right heart catheterization studies were carried out in a mildly sedated post absorptive state. Cardiac output was determined according to the Fick principle with mixed venous blood samples obtained from the pulmonary artery Blood oxygen

From the Division of Cardiology Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif.
Supported in part by United States Public Health Service Grant (HE 5440) and the Santa Clara Heart Association.
Received for publication March 20, 1967
*Professor of Medicine, Stanford University School of Medicine, Palo Alto, Calif Address Cardiology Division, C. 228, Stanford Medical Center 300 Pasteur Drive, Palo Alto, Calif 94304.
**Attending staff, Department of Cardiology Presbyterian Medical Center San Francisco, Calif
***Professor of Surgery Stanford University School of Medicine, Palo Alto, Calif.

content was determined with a reflection oximeter (American Optical Company) and expired air was analyzed in a Scholander apparatus. Intravascular pressures were referred to the mid-chest. After resting studies had been completed supine exercise was carried out for six minutes with a cycle ergometer (Enraco) fixed to the end of the fluoroscopic table. The mean exercise oxygen consumption was 115 to 177 per cent, that of the mean resting level in postoperative and preoperative studies, respectively. Cardiac output was determined and pressures were recorded during the final two minutes of exercise. The patient then rested quietly for 15 minutes. Isoproterenol was then infused intravenously at a rate of 203 gamma per minute for six minutes. The previous measurements were repeated from the fourth to the sixth minute. The chronotropic effect of the drug was evident in all patients and heart rates were comparable to those achieved during exercise. Normal values used for comparison with the data obtained in this study were obtained from previously published reports with appropriate corrections for age.[6-11]

Results

Despite marked subjective and objective improvement following operation no patient in this group had a perfectly normal exercise tolerance. While ordinary activities were performed without discomfort moderate effort evoked a sensation of fatigue weakness, and occasionally moderate dyspnea. None of the patients had clinical evidence of congestive failure. Hemodynamic studies revealed a resting pulmonary artery wedge pressure of 10 mm. Hg or less in all but two patients (mean 8.5 mm. Hg). The pulmonary artery mean pressure at rest was slightly elevated (mean 21.5 mm. Hg). The resting cardiac index was low (mean 2.56 L. per minute per square meter) and the arteriovenous oxygen difference was elevated (mean 5.40 ml. per 100 ml.) The cardiac output response to exercise when assessed in terms of the oxygen consumption was less than normal (7 per cent increase compared to a predicted increase of 41 per cent). The arteriovenous oxygen difference during exercise evaluated in a similar manner was greater than predicted. Pulmonary artery wedge pressure and mean pulmonary artery pressure rose to abnormal levels during exercise (19.4 and 38.7 mm. Hg respectively). Pre and postoperative data are summarized in Tables I and II and Figs. 1 and 2. The cardiac output response to the infusion of isoproterenol was, however normal and the pulmonary artery wedge pressure and the pulmonary artery mean pressure did not become abnormally elevated. Changes in heart rate produced by the infusion were similar to that produced in previous studies of the effect and of isoproterenol in normal subjects and in patients with mitral valve disease.[1, 11] The response to isoproterenol is summarized in Table III.

Discussion

Late hemodynamic studies following mitral valve replacement have been performed by five groups of workers whose data are summarized in Table IV. More recently observations have been made immediately after the operation and for the first few days of the postoperative period.[17, 1]

The most striking and important beneficial effect of mitral valve replacement operation is the marked fall in left atrial pressure to normal values in nearly all patients. The mean resting wedge or left atrial pressure in four groups of patients with the Starr Edwards prosthesis is 10.0 mm. Hg (Table IV). This has not been consistently observed following conventional closed techniques of mitral valvotomy. While conventional methods have resulted in a comparable decrease in left atrial pressure in many patients, a moderate elevation still persists in some patients due to incomplete relief of mitral valve obstruction. For example Donald and his workers[19] observed a mean pulmonary artery wedge pressure of 22.4 mm. Hg two years after mitral valvotomy in patients judged to have an excellent or very good result. The pressure was higher in those who have a less satisfactory result. Baker and Hancock[21] reported a more favorable result of closed valvotomy in 26 patients. A total of 15 had a mean postoperative pulmonary artery wedge pressure of 12 mm. Hg but in the remain-

Table I. Hemodynamic data in 22 patients prior to mitral valve replacement surgery

N	Initial	Sex	Age	Lesion	Rhythm	PAm (mm Hg) R	PAm (mm Hg) E	PAw (mm Hg) R	PAw (mm Hg) E
1	J B	F	47	MS MI	AF	33	58	19	33
2	J K	M	56	MI	AF	39	—	26	—
3	F C	F	34	MS MI	AF	29	49	22	41
4	R B	M	54	MS	AF	—	—	14	
5	L A	F	39	MI	AF	36	—	20	—
6	A B	F	39	MI	S	27	—	24	
7	R B	F	57	MS	S	38	69	21	—
8	J I	M	40	MS	AF	66	—	33	—
9	B S	F	48	MS MI	AF	30	58	16	28
10	H M	F	60	MS MI	AF	27	—	16	—
11	G B	M	54	MS MI	AF	46	—	38	—
12	C M	M	56	MI	AF	27	31	15	17
13	I O	F	55	MI	AF	35	—	24	—
14	R W	F	56	MI	AF	51	71	27	47
15	G M	M	54	MI	AF	31	47	20	30
16	B S	F	40	MS	AF	N preoper [illegible] study			
17	J J	M	48	MS MI	AF	27	—	24	—
18	L B	F	40	MS	AF	25	56	16	38
19	H M	M	41	MS	AF	19	52	12	30
20	L R	F	63	MS MI	AF	22	—	18	—
21	S M	M	54	MI	AF	41	—	23	—
22	S C	F	59	MS MI	AF	51	70	31	42
Mean			50			35	56 1	21 9	34 0
Range			34–63			19–66	31 71	12 38	17–47

Abbreviations. MS, mitral stenosis; MI, mitral insufficiency; AF, atrial fibrillation; S, sinus; PAm, pulmonary artery mean pressure; PA, pulmonary arteriolar resistance; BSA, body surface area; Vent, ventilation; R, rest; E, exercise.

ing patients the mean wedge pressure exceeded 16 mm Hg

The fall in pulmonary artery pressure and the decrease in pulmonary arteriolar resistance following valve replacement operation is equally striking and here also the results appear to be superior to those observed after closed mitral valvotomy.[14] A reduction in pulmonary ventilation during exercise also occurs which is usually correlated with relief of effort dyspnea.[29]

Despite these improvements in cardiac function two important residual abnormalities remain in all patients studied (1) a rise in pulmonary artery wedge pressure during exercise (2) a low cardiac output at rest and a subnormal cardiac output response to exercise.

The elevation of the pulmonary artery wedge pressure during exercise could be due to two factors (1) There could be obstruction to blood flow by the Starr Edwards prosthesis. Pressure gradients across the prosthesis were not assessed in the present study. Other workers have previously demonstrated that at rest a mean pressure gradient of approximately

C I (L./min./M)		*A V (ml /100 ml)*		*O_2 Cons (ml./min./M²)*		*PAR*	*BSA*	*Vent (L./min./M)*	
R	*E*	*R*	*E*	*R*	*E*	*U*	*M*	*R*	*E*
1 8	2 5	6 5	14 4	119	361	4 6	1 66	3 26	8 90
1 6	—	8 5	—	140		1 6	1 88	4 01	—
1 9	2 7	6 5	11 5	125	313	1 8	1 63	3 81	11 10
2 3	—	6 6	—	154	—	—	1 92	4 66	—
1 7	—	8 3	—	135	—	6 5	1 46	3 48	—
2 5	—	5 6	—	140	—	1 0	1 31	3 46	—
2 2	2 9	6 0	12 3	134	357	4 6	1 63	2 96	8 33
1 9	—	8 8	—	182	—	9 1	1 90	5 90	—
2 2	2 3	6 3	9 6	139	226	3 7	1 73	2 91	4 46
1 4	—	7 3	—	95	—	5 5	1 42	3 30	—
2 1	—	7 5	—	161	—	2 2	1 74	5 22	—
2 1	2 8	7 6	10 0	158	282	2 7	2 12	4 70	—
2 9	—	5 6	—	163	—	2 6	1 45	5 90	—
1 5	1 0	10 0	13 6	145	133	12 0	1 35	4 10	6 10
1 0	2 0	7 9	15 5	76	291	8 4	1 34	2 76	10 83
2 8	—	5 7	—	152	—	1 0	2 00	4 11	—
2 0	3 5	6 2	11 6	121	390	2 8	1 56	3 23	9 45
1 7	2 4	6 4	—	—	—	2 4	1 72	—	—
2 6	—	6 2	—	160	—	1 0	1 61	4 86	—
1 5	—	8 5	—	125	—	6 7	1 81	3 10	—
2 1	2 9	5 9	10 6	124	305	6 0	1 55	2 90	7 50
2 0	2 5	6 61	12 12	137	295	4 31	1 66	3 93	8 34
1 0–2 9	1 0 3 5	1 0–8 8	9 6–15 5	76–182	133–390	1 0 12 0	1 31 2 12	2 76–5 90	4 46–11 10

mean pulmonary artery wedge pressure C I cardiac index A V arteriovenous oxygen difference O_2 Cons oxygen consumption PAR

4 4 mm Hg is present across the prosthesis. This increases to a mean value of 12.3 mm Hg during moderate exercise.[4-6] This would appear to be responsible for most of the elevation in pulmonary artery wedge pressure during exercise in the patients in the present study. The failure of the pulmonary artery wedge pressure to rise significantly when cardiac output was increased by an infusion of isoproterenol suggests that obstruction to blood flow by the prosthetic valve may not be the only factor in producing a raised wedge pressure during exercise. (2) There could be elevation of left ventricular diastolic pressure. Direct measurement of left ventricular diastolic pressure following mitral valve replacement has been made by three groups of workers and slightly elevated resting values were frequently observed with a further rise during exercise. Rockoff and associates[22] reported resting values of 10 to 18 mm. Hg (mean 14 1 mm Hg) in ten patients who had no angiographic evidence of regurgitation around the prosthesis. Morrow and co-workers[4] reported a mean value of 6.5 mm Hg at rest and 8.5 mm. Hg during exercise. Judson and

Table II Hemodynamic data in 22 patients following mitral valve replacement surgery Range of Banchero and associates[1] and Donald and co-workers

No	Pt	V h cm	Rhythm	PAm R	PAm E	P 1w R	P 1w E	C.I R	C.I E
1	J B	3M	AF	21	32	6	12	1 9	2 9
2	J K	3M	AF	16	48	13	32	2 0	3 3
3	F C	2M	AF	19	38	9	22	2 7	2 6
4	R. B	2M	AF	14	31	8	21	1 4	2 3
5	L. A.	3M	AF	18	43	7	16	3 4	4 7
6	V B	3M	AF	24	—	—	—	3 5	—
7	R. D	2M	S	29	48	11	13	3 5	3 8
8	J F	2M	AF	19	34	10	17	3 0	3 7
9	B S.	2M	AF	27	46	8	12	2 1	2 6
10	H M	2M	AF	17	40	6	24	1 4	2 4
11	G B	33I	AF	22	38	10	31	2 4	3 5
12	C M	4M	AF	24	—	—	—	2 5	3 6
13	L O	3M	S	14	29	7	9	3 3	4 5
14	R W	2M	AF	27	61	9	23	2 6	3 9
15	G M	4M	S	16	37	5	14	2 5	4 0
16	B S	2M	AF	20	48	9	22	2 1	3 8
17	J J	4M	AF	23	39	8	19	2 6	3 8
18	L B	2M	S	25	35	10	24	2 9	4 1
19	H M	3M	AF	16	22	10	20	2 6	3 9
20	L R.		AF	20	33	6	21	1 9	3 5
21	S M		AF	14	27	3	9	2 1	5 1
22	S. C		S	30	45	14 5	26	3 9	6 8
Mean				21 5	38 7	8 5	19 4	2 56	3 76
Range				14–42	22–61	3–15	9–32	1 4 3 9	2 4–6 8

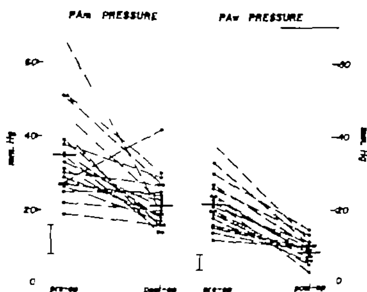


Fig. 1 Mean pulmonary artery pressure and mean pulmonary artery wedge pressure before and after mitral valve replacement surgery The range of normal values is indicated by the brackets.

normal values indicated below are obtained from references referred to in this paper and data of

A V		O_2 Cons		PAR	Vent.		Follow-up time (mo.)
R	E	R	E		R	E	
6 4	13 4	122	370	4 7	4 36	11 20	7
7 8	14 3	151	467	0 8	4 14	18 80	3
4 7	9 5	124	239	2 2	3 17	9 28	5
6 9	10 5	94	253	2 2	2 06	5 68	9 5
4 4	8 8	150	406	2 5	3 04	9 70	4
4 8	—	169	—	—	3 86	—	4
3 6	8 1	126	303	3 2	3 55	6 63	3
4 5	11 8	133	428	1 6	3 55	11 70	7
6 0	10 9	127	285	5 3	3 21	5 98	3
7 3	11 6	95	274	5 2	2 70	7 90	5 5
6 2	11 6	150	400	2 9	4 90	11 75	5
6 2	8 2	161	295	—	4 16	8 42	5
4 5	9 3	145	415	2 0	6 32	9 62	7
5 5	11 7	138	452	4 6	3 16	11 80	10
5 1	10 4	129	420	3 0	3 12	8 65	6
5 3	8 3	112	315	3 4	3 80	8 30	5
5 1	11 2	133	425	2 8	3 60	9 38	7
4 2	8 4	119	337	3 5	4 00	10 20	6
6 2	—	161	—	1 3	3 74	—	8
5 4	8 9	102	310	4 4	4 65	—	22
5 8	8 1	116	440	3 0	2 26	8 71	9
3 0	6 2	118	426	2 5	2 08	8 00	8
5 40	10 06	131	363	3 0	3 61	9 56	6 8
3 0–7 8	6 2 14 3	94 169	239–467	0 8–5 3	2 06–6 32	5 68–18 80	3–22

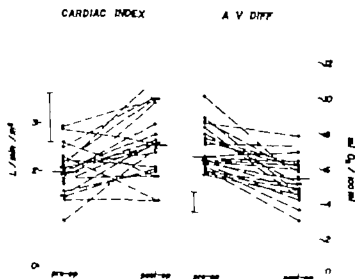


Fig. Cardiac index and arteriovenous oxygen difference before and after mitral valve replacement surgery The range of normal values is indicated by brackets.

Table III. Hemodynamic response to infusion of isoproterenol in patients following mitral valve replacement surgery. Mean values and range for all patients studied are presented

	Control		Isuprel	
	Mean	Range	Mean	Range
Mean PA pressure (mm. Hg)	19.6	14-30	22.4	13-31
Mean PA wedge pressure (mm. Hg)	8.2	3-15	8.0	1-13
Cardiac index (C.O./L./min./M.²)	2.6	1.4-3.9	4.1	2.6-5.8
Arteriovenous difference (ml./100 ml.)	5.3	4.2-7.3	3.7	2.5-4.9
Oxygen consumption (ml./M.²)	126	94-161	144	128-188
Heart rate	71	50-108	111	75-178
Pulmonary arteriolar resistance (units)	3.0	1.6-5	2.4	1.0-4.1

Table IV. Hemodynamic data in patients following mitral valve replacement surgery collected from published reports. Name of first author and bibliographic reference number given for each report

Author	PAm		P (w or LA)		Cardiac index		LVEDP		MV gradient	
	R	E	R	E	R	E	R	E	R	E
Present study	21.5	38.7	8.5	19.4	2.56	3.76	5.40	10.26		
Judson and co-workers	17	35	10	22	2.52	3.95	5.44	9.25		
Morrow and co-workers			9.3	18.0	2.86	3.69			4.4	8.7
Braunwald and co-workers	26		11.5		3.00					
Starr and co-workers	23	33	10	15	2.90	3.50				
Beck and co-workers*[10]	35	60	16.1	32.5	2.58	3.60			5.5	12.3
Mean	24.5	41.7	10.9	21.4	2.74	3.70	5.42	9.65	5.0	10.5

*University of Cape Town prosthesis.

associates observed a mean value of 6.4 mm. Hg in 12 patients. Beck and co-workers[10] reported a mean value of 9 mm. Hg at rest and 12 mm. Hg during exercise in patients with the University of Cape Town prosthesis. Similar observations were made in one patient (No. 20) included in this report. Left ventricular pressure was measured by retrograde catheterization 21 months after insertion of a 3M Starr-Edwards prosthesis. The resting mean diastolic pressure was 7.5 mm. Hg and during moderate supine exercise the pressure rose to 18.0 mm. Hg. Injection of 50 ml. of Renografin resulted in an elevation to 11.0 mm. Hg. Right heart catheterization studies 21 months after the operation had revealed a resting pulmonary artery wedge pressure of 6 mm. Hg, an exercise pressure of 21 mm. Hg, and a pressure of 8 mm. Hg during isoproterenol infusion. The hemodynamic response to isoproterenol supports the possibility that a rise in left ventricular diastolic pressure occurs during exercise following mitral valve replacement. If valve obstruction alone were the only cause of the rise in pulmonary artery wedge pressure during exercise, one

would expect a similar rise to occur during the infusion of isoproterenol which increases the cardiac output and heart rate to a similar degree. This is the response that is usually observed in patients with uncomplicated mitral stenosis prior to operation.[18] Isoproterenol infusion after mitral valve replacement however is not accompanied by an elevation of pulmonary artery wedge pressure. This is probably due in part to the positive inotropic effect of this drug upon left ventricular function resulting in a fall in left ventricular diastolic pressure.[13] Thus, present evidence suggests that the raised pulmonary artery wedge pressure during exercise in patients who have had mitral valve replacement operation is due partly to the obstruction of the prosthetic valve and partly due to a raised left ventricular diastolic pressure.

A second important abnormality in cardiac function following mitral valve replacement is a low cardiac output observed at rest and during exercise. The range of normal values is indicated in Table II and Fig. 2. The low cardiac output was not due to hypometabolism since the resting oxygen consumption was normal or slightly elevated. The arteriovenous oxygen difference was greater than normal at rest and during exercise suggesting a deficiency in cardiac function rather than a low oxygen consumption. Atrial fibrillation was not responsible since no significant difference in cardiac output was observed between patients with atrial fibrillation and those with sinus rhythm. Right ventricular failure was not present at rest or during exercise.

Is a low cardiac output and an elevation of left atrial pressure during exercise due to a leak around the prosthesis. Rockoff and his workers[22] have shown that regurgitant leaks around a mitral prosthesis may not be accompanied by an apical systolic murmur or any of the other usual signs of mitral insufficiency. In one patient in the present study a small leak was demonstrated by angiography but this patient had a Grade 1 full apical systolic murmur. None of the other patients in the series had apical systolic murmurs or any clinical evidence that a leak around the prosthesis was present. In none of the patients in this series was a V wave seen in the pulmonary artery wedge pressure tracings that would suggest the presence of a regurgitant leak. It seems unlikely in view of these observations that regurgitation around the prosthesis accounts for the cardiac dysfunction observed in the patients presented in this study.

Could the cardiac dysfunction be the result of myocardial fibrosis secondary to chronic rheumatic heart disease? Two observations make this an unlikely possibility. (1) Myocardial fibrosis in chronic rheumatic heart disease is rarely extensive and is usually localized to the adventitia of the blood vessels.[23,24] Such changes do not seem sufficient to interfere with cardiac function. (2) A total of 19 patients studied in this laboratory following aortic valve replacement operation for aortic stenosis or aortic insufficiency did not demonstrate the abnormalities in pulmonary artery wedge pressure or cardiac output observed in the patients with mitral valve replacement.[25] Comparable observations have been made by others.[26,27] Similar differences between patients with mitral valve replacement and those having aortic valve replacement have been observed in the immediate postoperative period.[3,4] If rheumatic myocardial disease was functionally important similar abnormalities in cardiac function should be seen in both groups since a majority of patients with aortic valve replacement have clear evidence of chronic rheumatic valvular disease.

Is cardiac dysfunction following mitral valve replacement operation due to loss of papillary muscle function. In the technique of mitral valve replacement at this institution the chordae are severed at their junction with the tips of the papillary muscles. The important function of these muscles in left ventricular performance has been described.[28,29] Loss of this function could result in a low cardiac output and a rise in left ventricular diastolic pressure during exercise. Lillehei and his workers[30] employ a technique of mitral valve replacement which preserves the continuity of both papillary muscles and their chordae. A lower postoperative mortality rate has been observed using this technique and it is claimed that left ven

tricular function is more normal following the procedure. No hemodynamic data have been presented to support this contention however Bjork and associates[21] have presented data suggesting that left ventricular function is not impaired following mitral valve replacement operation. Left ventricular angiograms were performed in five patients prior to the operation and from one to two years later In two there was a decrease in systolic and diastolic left ventricular volume but in three these volumes were essentially unchanged More recently Kirklin and his associates[22] have shown that in dogs a Starr Edwards prosthesis with excision of the papillary muscles did not result in demonstrable impairment of cardiac function at rest or during vasodilatation by intra arterial acetylcholine infusion Heart rates during exercise two months after operation were similar to those observed in control animals. The above observations are not sufficient to determine the precise hemodynamic effect of loss of papillary muscle function in man however Thus, while loss of papillary muscle function would appear to be a possible factor limiting cardiac performance following mitral valve replacement surgery this concept remains unproved

If a limitation of cardiac output is an important abnormality in the valve replacement group this may be comparable to that seen in patients with mitral stenosis in whom this has appeared to be the most important functional abnormality The data from 11 patients previously reported in the literature as examples of mitral stenosis with an important myocardial factor limiting cardiac performance have been reviewed[23-25] Pressures at rest and during exercise and calculated pulmonary arteriolar resistances are comparable to those in patients following mitral valve replacement. The cardiac output was lower in patients with a myocardial factor at rest and during exercise but this was related to a lower oxygen consumption in this group The A V difference at rest in the two groups was comparable and the A V difference during exercise was actually lower in the patients with a myocardial factor compared to the valve replacement group These data support the suggestion previously made in this paper that an important factor is present in patients who have had mitral

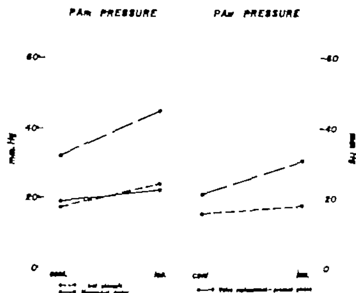


Fig 3 The effect of isoproterenol I fusion poo the pulmonary artery mean pressure and the pulmonary artery wedge pressure in patients w th mitral valve replacement. For comparison data obtained on patients with uncomplicated m tral stenosis and patients ith myocardial factor" are included as obtained from studies by Cox and associates.[24]

valve replacement operation that limits cardiac output.

The response of heart rate, cardiac output and oxygen consumption to isoproterenol infusion in the mitral replacement group was essentially normal.[1-11] No significant rise in pulmonary artery pressure or pulmonary artery wedge pressure was observed. This response is not seen in mitral stenosis. Cox and his workers[11] have studied the hemodynamic effect of isoproterenol infusion on patients with uncomplicated mitral stenosis and patients with mild mitral stenosis in whom a low cardiac output was considered to be due to a myocardial factor. Their data are summarized in Fig. 3 with data obtained in the present study. It is clear that in patients with mitral stenosis, isoproterenol infusion is associated with a sharp rise in pulmonary artery and wedge pressure. Patients with a myocardial factor limiting cardiac output and patients who have had mitral valve replacement operation demonstrate only a slight rise in pulmonary artery and wedge pressure. These data also demonstrate a clear similarity between patients who have a myocardial factor limiting cardiac performance and patients who have had mitral valve replacement surgery.

It is evident from the studies reported in this paper as well as data obtained by other workers, that cardiac dysfunction is present in patients following mitral valve replacement operation. The most important abnormality is a low resting cardiac output and a subnormal response of cardiac output to exercise. A similar abnormality is present in patients with mild mitral stenosis in whom a myocardial factor limits cardiac performance. It is possible that these patients possess in common some fixed abnormality either in the myocardium or in the control of cardiac output. The possibility of deficiency of papillary muscle function cannot be entirely dismissed but direct evidence supporting this possibility is lacking.

Summary

1. Hemodynamic studies have been performed in 22 patients assessed as having had an excellent result from mitral valve replacement surgery.

2. Following mitral valve replacement a striking decrease in pulmonary artery pressure, pulmonary artery wedge pressure, and pulmonary arteriolar resistance was observed. Cardiac output increased and the cardiac output response to exercise was improved.

3. Residual abnormalities in cardiac function remain, however. Pulmonary artery wedge pressure becomes elevated during exercise, the cardiac output at rest is low, and the increase of cardiac output during exercise is less than normal.

4. The cause of the hemodynamic dysfunction following mitral valve replacement surgery is not clear. Loss of papillary muscle function incident to surgery as a possible mechanism has been reviewed.

5. Although the hemodynamic improvement in selected patients with closed or open valvotomy approximates that obtained with valve replacement surgery, the success of valve replacement techniques in patients with mitral insufficiency and severe mitral valve disease not amenable to nonreplacement techniques constitutes a striking advance in cardiovascular surgery.

REFERENCES

1. Starr, A.: Total mitral replacement: Fixation and thrombosis, S. Forum 11:258, 1960.
2. Starr, A., and Edwards, M. L.: Mitral replacement: Shielded ball valve prosthesis, J. Thoracic & Cardiovas. Surg. 42:673, 1961.
3. Starr, A., and Edwards, M. L.: *Mitral replacement*: Clinical experience with a ball valve prosthesis, Ann. Surg. 5 727 1961.
4. Starr, A., Edwards, M. L., and Griswold, H.: Mitral replacement: Late results with a ball valve prosthesis, Progr. Cardiovas. Dis. 5:298, 1962.
5. Judson, W., Ardaiz, J., Strach, T., and Jennings, R.: Postoperative evaluation of prosthetic replacement of aortic and mitral valves, Circulation (Suppl. 2) 29:14, 1964.
6. Morrow, A., Clark, W., Harrison, D., and Braunwald, E.: Prosthetic replacement of the mitral valve, Circulation (Suppl. 2) 29:2, 1964.
7. Braunwald, E., Braunwald, N., Ross, J., and Morrow, A.: Effects *of mitral valve replacement* on the pulmonary vascular dynamics of patients with pulmonary hypertension, New England J. Med. 273:509, 1965.
8. Iben, A., Hurley, E., and Shumway, N.: Surgery for combined lesions of the aortic and mitral valves, Am. J. Surg. 110:262, 1965.
9. Braunwald, E.: Clinical cardiopulmonary physiology, New York, 1960, Grune & Stratton, Inc.
10. Reeves, J., Grover, R., and Blount, S.: Circula

and the tip positioned in the mid abdominal vena cava. In order to avoid fibrin deposition which greatly reduces the sensitivity of the system the catheters were treated with Monocote E.* The flow determinations were performed at the conclusion of routine diagnostic catheterizations, preparatory to surgical correction with fully informed consent from the patient or parents.

Seven patients with tetralogy of Fallot were studied ranging in age from 10 months to 23 years (Table I). Exercise in five older patients was performed on a bicycle ergometer in the supine position until the oxygen saturation had dropped appreciably measured with an earpiece oximeter. After discontinuation of exercise the subjects kept their legs level with their body until they were placed in a knee-chest position with the thighs and knees flexed maximally. The patients were assisted in holding the knee-chest position by an attendant. When the position was discontinued the legs were returned to a level supine position. In the younger patients exercise was not performed and only the effects of the knee-chest position were studied.

The 23-year-old patient was studied a second time during treadmill exercise with blood samples from the radial artery. The samples were analyzed for oxygen saturation with a Wood's cuvette oximeter and for lactate. The treadmill exercise was performed at zero grade and 2 miles per hour for 10 minutes, and the patient was permitted to squat.

Results

In every instance assumption of the knee-chest position produced a sustained decrease in flow in the IVC usually preceded by a transient increase in flow (Table I). Returning to the supine position caused a consistent increase in flow relative to the knee-chest position (Fig. 1).

Oxygen saturation behaved in a less consistent manner depending upon the severity of the patient's disability, intensity, and duration of exercise (Fig. 2, 3). The oxygen saturation fell in every case with exercise and regardless of the patient's condition or position there was a gradual recovery toward normal after discontinuation of exercise. In the patients who exercised to the point of fatigue and breathlessness, squatting produced a prompt improvement in saturation. For example, with an exceptionally cooperative 13-year-old girl the arterial saturation was 94 per cent at rest and fell to 87 per cent with exercise. Knee-chest position caused an immediate increase to 93 per cent, and after two minutes the saturation was 94 per cent. Straightening the legs in the supine position after exercise caused a drop to 90 per cent.

The adult patient with exercise on a treadmill demonstrated a profound drop in arterial saturation and a significant increase in arterial lactate (Fig. 4). Squatting produced a prompt decrease in the lactate and an increase in saturation which were reversed by resuming the erect posture.

Discussion

Some of the apparent conflict between previous publications stems from dissimilar uses of the term venous return. Pooling in the legs may be prevented by squatting but squatting cannot produce a sustained increase in venous return in the IVC. A reservoir of blood can be emptied to provide a brief increase in venous return[13] and this increment may substantially add to the central blood volume[8] and the filling pressure of the right and left ventricles.[1] However in order to have a sustained increase in venous return from any part of the vasculature an increased arterial input is a necessity. Brotmacher[7] demonstrated that arterial input to the legs is diminished by squatting.

Relative to squatting there is no question that the position is effective against syncope after marked exertion even in the normal person. Quiet standing particularly after exercise can pool considerable quantities of blood in the legs.[11] Furthermore, the tendency to faint in the normal person is exaggerated by hypoxia.[12] Squatting is an effective means of counteracting the effects of orthostatic hypotension and this may be a significant advantage of squatting or simply lying down in many patients with tetralogy of Fallot.

*Available from Armour Pharmaceutical Company.

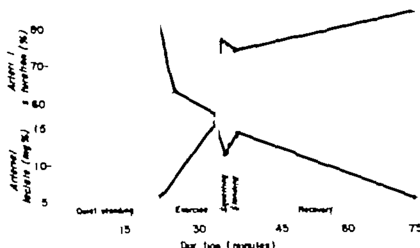


Fig. 4. Graph of arterial saturation and lactate with exercise and squatting in the upright position in 23 year old patient. With exercise there is drastic reduction in saturation and an increase in lactate. Squatting improves the saturation and lowers the lactate, indicating reduction of flow to the leg muscles with corresponding diminution of venous return. Exercise was carried out on level treadmill at 2 m.p.h. for 10 minutes.

The existence of postural hypotension does not explain all of the effects of squatting as shown by the changes produced by the knee-chest position. The knee-chest position has been shown to diminish flow into the legs, or as a corollary to diminish venous return as in this study. The reduction of venous return from postexertional leg muscles will cause a substantial increase of saturation of blood in the right side of the heart resulting in an improved arterial saturation even if there is no change in right to-left shunting. Brotmacher[7] found that after vigorous arm exercise squatting failed to improve the arterial saturation indicating the specific effect of squatting on reducing venous return from a vascular bed which has extracted a large percentage of the available oxygen. The sequence of arterial lactate levels shown in Fig. 4 offers additional evidence of the specific effect of squatting in reducing venous return from an active muscle bed. Squatting lowered the arterial lactate from 13.5 to 11 mg. per cent while it increased the arterial saturation from 57 to 77 per cent. The improvement in arterial lactate, oxygen saturation and probably pCO_2 would also have an effect of decreasing the chemical stimuli for respiration and may account for improvement in the subjective state of breathlessness and may assist in aborting paroxysmal hyperpnea or blue spells.

Increased systemic vascular resistance should provide additional benefit to recovery in these subjects by increasing pulmonary blood flow since the major resistance to flow through the pulmonary circuit is relatively fixed by the congenital obstruction.[4,5] If significant pooling occurs with the erect posture, squatting may improve the effective filling of the right ventricle which may result in a reduction of resistance to outflow of a narrow infundibulum through a larger diastolic volume. This mechanism does not appear to operate in the supine knee-chest position since there is a sustained *decrease* in inferior caval flow.

Squatting does not, of course, alter the "oxygen debt" after exercise but it does permit repayment over a longer period. The vascular beds of active muscle groups remain dilated after exercise and the flow persists at levels almost equal to those during exercise (Fig. 3). Squatting does not abolish flow to the legs, but reduces it to the resting level, prolongs the recovery period for active muscles, and improves the state of the organism during recovery.

Conclusions and summary

An isothermal thermistor mounted on a cardiac catheter has been used to study the flow in the IVC in the supine knee-chest position in seven patients with tetralogy of Fallot In every instance, the knee chest position produced a sustained de crease in flow in the cava, usually preceded by a transient increase One adult patient was restudied with erect exercise squatting improved the arterial saturation and lac tate indicating a reduction in venous re turn from the active muscles in the legs.

There are probably three benefits of squatting (1) Syncope may be prevented by squatting or simply assuming a re cumbent position Patients with tetralogy of Fallot are probably unusually liable to syncope due to hypoxia. (2) Squatting or the knee-chest position produces a su stained reduction in venous return from the legs and after exercise the effluent from active muscle groups has a markedly low oxygen satu ation The saturation of the m xed systemic venous return consequently will rise with squatting and the systemic arterial saturation will be improved even if there were no change in the volume of the right to-left shunt. (3) There appears to be an ncrease in systemic vascular re sistance with squatt ng and a rise in the common ventricular pressure permitting an ncrease in pulmonary blood flow

W sh to thank Dr W llard P Johnson for his assistanc in the study of the adult patient, and Doctor M ng Park and Courtney Anthony for their assistanc th several of the ch ldren

REFERENCES

1 H nter W Three cases of malform tions of the heart Medical Observations nd Inquiries by a Society of Physicians in London 6:291 1784
2. Lurie P R. Postural effects in tetralogy of F llot, Am J Med 15:297 1953
3. Keith, J D Rowe, R D and Vlad, P Heart disease in infancy nd childhood, New York, 1958 MacMillan Company p 402.
4 Taussig H B. Congenital malformation of the heart, ed. 2, Cambridge 1960, Harvard University Press, p. 23.
5 Cailebaut, C Denolin, H. and Lequime, J Recherches oxymetriques dans les cardiopathies congénitales, Acta cardiol. 4:324, 1949
6. Hamilton, W F Winslow J A and Hamilton, W F J Notes on a case of congenital heart disease ith cyanotic episodes, J Clin. Invest. 29:20 1950
7 Brotmacher L. Haemodynamic effects of squatting during recovery f om exertion, Brit. Heart J 19:567 1957
8 Nadas, A. S Pediatric cardiology ed 2, Philadelphia, 1963 W B. Saunders Company p. 353.
9 O Donnell, T V nd M Ilroy M B The circulatory effects of squatting Am Heart J 61 347 1962.
10. Sharpey Schafer E. P Effects of squatting on the normal and failing irc lation Brit. M J 1 1072, 1956
11 Mellander S and Rushmer R. F Venous blood flow recorded th an sothermal flow meter Acta physiol. scandinav 48 13, 1960.
12. Katsura, S. Weiss, R Baker D nd Rushmer R. F Isothermal blood flow velocity probe, IRE Transaction on Medical Electronics, ME 6:283, 1959
13. Guntheroth, W G and Mullins, G L. Liver and spleen as venou reservoirs, Am. J Physiol 204:35 1963
14 Morgan, B. C Guntheroth, W G., and M Gough, G. A. Effect of position on leg volume case against the Trendelenburg position, J A. M A. 187 1024 1964.
15 Stead, E A., J Fainting Am. J Med. 13:387 1952
16. Guntheroth, W G. Morgan, B. C., nd Mullins, G L. Physiologic studies of paroxysmal hyperpnea in cyanotic ongenital heart disease, Circulation 31 70, 1965.

"Polarizing" solutions in patients with acute myocardial infarction

A double-blind study with negative results

Gerald F. Fletcher, M.D.
*J. Willis Hurst, M.D.***
*Robert C. Schlant, M.D.***
Atlanta, Ga.

"Polarizing" solutions of glucose, insulin, and potassium are currently used in the therapy of acute myocardial infarction. A number of reports supporting the value of this type of therapy have stated that patients receiving this solution had more rapid evolution of the electrocardiogram (ECG), fewer arrhythmias, and fewer deaths. However, other observations have shown that treatment with such solutions has not resulted in improvement or has perhaps resulted in an increased incidence of arrhythmias.

Because of this controversy, a double-blind controlled study was designed to evaluate the effect of the three components of the solution singly and in combination upon the ECG, incidence of arrhythmias, and mortality rate of patients with acute myocardial infarction.

Method and materials

Patients admitted to the medical service of Grady Memorial Hospital, Atlanta, Georgia, with a typical history and electrocardiographic changes of acute myocardial infarction were selected for the study. All of these patients had S-T segment and T wave changes; most of them had QRS segment changes. Contraindications for admission to the study group were patients with shock, severe renal insufficiency, second-degree and complete heart block, severe pulmonary edema, and diabetic patients receiving insulin. Five different study variables (four different solutions) were used; patients receiving insulin were given 40 units daily and those receiving potassium were given 80 mEq. of potassium chloride daily. It was felt that 80 mEq. of potassium chloride could be safely tolerated by the patients over a 24 hour period.

The five study regimens used were: (1) no solution—control (C); (2) glucose, 10 per cent in water (G); (3) glucose, 10 per cent in water with 40 units of insulin per liter (GI); (4) glucose, 10 per cent in water with 80 mEq. of potassium chloride per liter (GK); and (5) glucose, 10 per cent in water

From the Department of Medicine, Emory University School of Medicine and the Medical Service of Grady Memorial Hospital, Atlanta, Ga.
Received for publication May 2, 1967.
*Research Fellow in Medicine (Cardiology), Emory University School of Medicine.
**Professor and Chairman, Department of Medicine, Emory University School of Medicine, and Chief of the Medical Service, Grady Memorial Hospital.
***Professor of Medicine (Cardiology), Emory University School of Medicine.

with 80 mEq of potassium chloride per liter and 40 units of insulin per liter (GIK)

Patients were grouped by means of a random selection double blind method as devised with the Department of Biometry of Emory University. Solutions were prepared by a research assistant as determined by the code. Groups 2 through 5 received 1 L. of solution daily for three days; daily solutions were given as constant infusions for 24 hours. This volume and rate of infusion was felt to be safe for the patient. The patients had at least daily ECGs, daily serum electrolyte determinations, and frequent clinical observations. Continuous oscilloscopic monitoring was used in 40 patients and memory tape (magnetic tape recording of significant slowing or speeding of cardiac action) was employed in 21 patients. The solution was stopped if the patient developed second degree or complete heart block.

Results

A total of 80 patients met the specified criteria and were included in this study. Of all the patients, 56 per cent were Caucasian men; the remainder were fairly evenly distributed as regards race (Caucasian and Negro) and sex. The average age of the patients was 57.6 years; the age range was 31 to 83. The apparent location of the infarction was anterior in 55 per cent of the patients, inferior in 40 per cent, and subendocardial in 5 per cent.

The electrocardiographic changes are seen in Fig. 1. Although there was no statistically significant difference in the five groups studied, it is notable that 56 per cent of the GK and GIK groups had "progression" of their electrocardiographic changes. ("Progression" in this text refers to persistance of ST segment changes for more than the usual two or three days or to further development of ST changes during the course of treatment.) Less than 20 per cent in each of these groups had "regression" of their electrocardiographic changes. ("Regression" refers to a decrease in the amount of ST segment displacement or return of the ST segment displacement to the baseline in less than two or three days.)

Arrhythmias are tabulated in detail in Fig. 2. There was no significant difference in the five groups studied. However, it is interesting that the three tachyarrhythmias occurring in the 80 patients studied were in

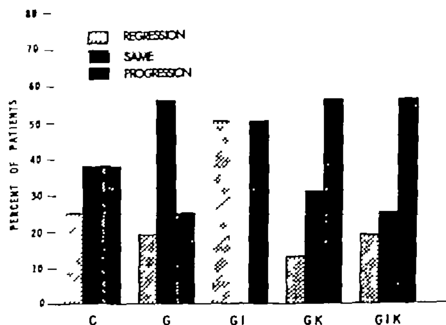


Fig. 1. Bar graph showing electrocardiographic changes. Note that 56 per cent of the patients in the GK and GIK groups had "progression" of electrocardiographic changes. *C*, No solution; *G*, glucose; *GI*, glucose and insulin; *GK*, glucose and potassium; *GIK*, glucose, insulin, and potassium.

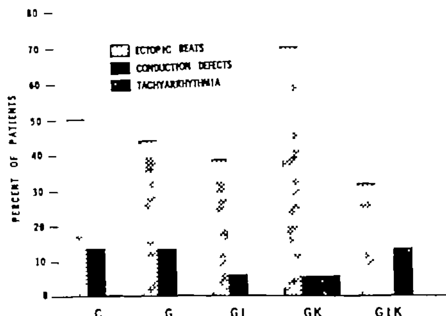


Fig. 2. Bar graph showing arrhythmias. Note that the three tachyarrhythmias were in the *GK* and *GIK* group. Also 69 per cent of the patients in the *GK* group had ectopic beats. *C*, No solution; *G*, glucose; *GI*, glucose and insulin; *GK*, glucose and potassium; *GIK*, glucose, insulin, and potassium.

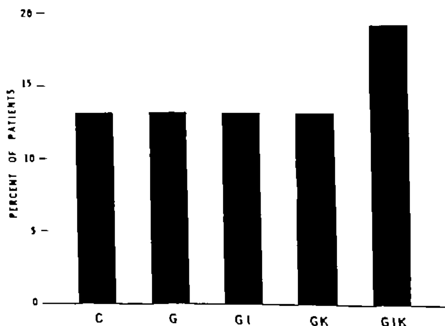


Fig. 3. Bar graph showing mortality. Note the mortality rate was 13.7 per cent in the *GIK* group as opposed to over-all figure of 19 per cent. *C*, No solution; *G*, glucose; *GI*, glucose and insulin; *GK*, glucose and potassium; *GIK*, glucose, insulin, and potassium.

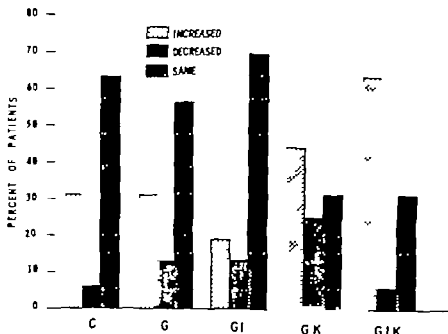


Fig 4 Bar graph showing serum potassium changes. Note that 63 per cent of the *GIK* group had an increase in serum potassium. *C* N solution *G* glucose *GI* glucose and insulin *GK* glucose and potassium; *GIK* glucose insulin and potassium

the GK and GIK groups (one and two respectively)

The mortality rate is shown in Fig 3 Of 11 deaths in the 80 patients studied three occurred in the GIK group (19 per cent) The over all mortality rate was 13 7 per cent

Serum potassium changes are tabulated in Fig 4 Note that 63 per cent of the GIK *treated patients had an increase (0 6* mEq per liter or more) in serum potassium as opposed to the control group in which 63 per cent had no change.

Discussion

In this study there was no statistical difference between the five groups in the incidence of electrocardiographic changes arrhythmias, or mortality rate these findings are in contrast to some previous experimental animal studies and clinical studies.

In 1957 Jennings and associates[7] showed in dogs that experimental coronary occlu*sion caused almost complete loss of* potassium from the myocardial cell in 12 to 15 hours. In 1958 Selye[8] stated that magnesium chloride and potassium chloride protected the myocardium from toxic agents such as papain and prevented experimental arteriosclerosis in cats. Sodi-Pallares and associates[4] have reported that in experimental myocardial infarction in dogs, the ECG showed rapid disappearance of the signs of injury in those treated with polarizing solutions and infarctions were much smaller in the treated animals. In 1965 however Dixon and associates reported no beneficial or deleterious effects of GIK infusion in dogs when the infusion was begun simultaneously with ligation of the anterior descending coronary artery

In 1957 Gubner and Behr[1] reported that the administration of potassium chloride to patients with coronary disease prevented ischemic electrocardiographic changes, relieved coronary pain and increased exercise tolerance.

Sodi Pallares and associates[1] later treated 34 patients with angina pectoris with oral potassium chloride and felt it was symptomatically beneficial In 1962 he reported the polarizing treatment of ten patients *with acute myocardial infarction He used* solutions of glucose (10 per cent) in water with 40 mEq of potassium chloride and 20 units of regular insulin per liter He believed that the solution caused more rapid evolu

tion of the infarction more rapid stabilization of the ECG a decrease in arrhythmias, a sense of well-being in the patient and relief of pain.[11] In 1963 he reported 50 patients with acute myocardial infarction of whom 25 were treated with glucose insulin and potassium solutions and 25 served as control In these, he again believed that the ECG stabilized more rapidly and arrhythmias, pain shock, and congestive heart failure were less frequent among the treated In 1965 Mittra[3] reported 170 patients with acute myocardial infarctions of whom 85 were treated with potassium chloride, glucose orally and insulin subcutaneously The remaining 85 served as controls Mortality rate was decreased by 16 5 per cent in the treated group Day in the same year stated that 33 patients were treated with the Sodi Pallares regimen and the house staff was impressed with the recovery and well being of these patients.

A preliminary evaluation on the present study was reported in 1966 and at that point there was no significant difference between the GIK treated group of patients and the control group Malach recently reported that 65 per cent of patients receiving polarizing therapy had life threatening arrhythmias as compared to an incidence of 15 per cent such arrhythmias in a control group that received glucose only In his study the mortality rate was similar between the groups (12 7 per cent in the polarizing group and 14 8 per cent in the control group)

The shortcomings of the study reported here are readily apparent. Constant oscilloscopic monitoring was not used in all patients and even in those patients monitored in an intensive care unit, it required about three seconds of slow or rapid heart action to trigger the automatic graphic recorder Thus, some arrhythmias, particularly of short duration could have been missed unless observed on the oscilloscopes at the bedside at the nurse s console of the intensive care unit or on serial ECG s. Also the solutions used were different from those of previous studies and our criteria for admission to the study excluded a number of patients with myocardial infarction both of these factors may have influenced our results.

Although there is no statistically significant difference between the five groups studied some interesting points can be mentioned The ECG had expected changes (S-T segment resolution in two to three days with concurrent T wave inversion) in 56 per cent of the G group whereas 56 per cent of the GK and GIK groups had progression of their electrocardiographic changes. Sixty nine per cent of the GK group had ectopic beats and two of the three tachyarrhythmias were in the GIK group The mortality rate was 19 per cent in the GIK group as compared to the over all mortality rate of 13 7 per cent. The serum potassium increased during therapy (in the range of 0 6 to 2.3 mEq per liter) in 63 per cent of the GIK group One patient in this group required treatment for hyperkalemia (serum potassium 7 7 mEq per liter) and an associated nodal rhythm another had the solution discontinued because of a serum potassium of 8.0 mEq per liter

Not infrequently the solutions containing potassium caused pain and/or inflammation at the site of infusion. Because of this, the infusions had to be discontinued early in 25 per cent of the GK and GIK groups.

Although this study reveals no statistically significant difference between the groups treated in this especially selected group of patients, it is felt that the notable data mentioned preclude the *routine* use of GIK solutions in the treatment of acute myocardial infarction.

Summary

A total of 80 highly selected patients with classical findings of acute myocardial infarction have been treated with polarizing solutions in a double-blind controlled study The five groups comprising the study were no solution control glucose, glucose and insulin, glucose and potassium and glucose insulin and potassium Using the parameters, electrocardiographic changes, arrhythmias and mortality rate and with deference to the selection of patients, concentration of solutions and methods of monitoring we found no statistically significant difference in results between the five groups studied. There is, in addition no apparent evidence of benefit from the polarizing treatment, and it is felt that such solutions should

not be *routinely* used in the treatment of patients with acute myocardial infarction

W ould l ke t express our ppreciation t Dr Malcolm E. Turner nd Dr Lou D Homer of the Department of Biometry Emory U l ersity for thei help outl ning nd evaluati g this tudy

REFERENCES

1 Sodi-Pallares D Bisteni, A. Medrano, G A. Testell M R nd De Micheli, A The polar izing tre tment of acute myocardial infarction Possibil ty of its use in other cardiovascular conditions, Dis. Chest 43:424 1963
2 D y H. W Effectiveness of an I tensive coronary care area, Am J Cardiol 15:51 1965
3 M ttra, B Potassium, glucose, nd insulin treatment of myocardial farction, Lancet 2:607 1965
4 Sodi-Pallares, D Bisten A Medrano, G A De Micheli, A Ponce de Leon, J Cal a, E Fishleder B L Testelli, M R. nd M ller B L The polarizing treatment in cardiovascular condition Bajusz, E editor Electrolytes nd cardiovascular diseases, Basel, New York, 1966, S. Karger vol 2 p 198
5 Fletcher G. F Hurst, J W nd Schla t, R. C Preliminary report of double-blind controlled study of the use of polarizing solutions in acute myocardial infarction, Circulation 34 (No. 4 Suppl. III) 102, 1966
6. M lach, M Polarizing sol tion in acute myocardial I farction, Am. J Cardiol. 19 141 1967 (Abstr)
7 Jennings, R. B Grout J R nd Sonetters, G. W Studies on distribution nd localization of potassi m in early myocardial ischemic i j ry Arch. P th 63:586, 1957
8. Selye, H. The chemical prevention of cardiac necrosis, New York 1958 Ronald Press company
9 Dixon, S Hyde S Leonard R P nd Sch lant R C. Failure of glucose-insulin-potassium infusion t modify the consequences of acute coronary artery ligation, J of Thoracic & Cardiovas. Surg 19 762, 1965
10. G bner R. S and Behr D J Role of electrolytes i origin of ischemic cardiac pain nd associated electrocardiographic abnormal ties, Circulation 16:889 1957 (Abstr)
11 Sodi-Pallares, D Fishleder B L., Cisneros, F Vizcaino, M Bisteni, A., Medrano, G. A Polansky B. J and De Micheli, A A low sodium, high ter high potassium regimen in the successf l management of some cardiovascular diseases, Canad. M A.J 83:243 1960.
12. Sod P llares, D Testelli, M R., Fishleder B L Bisteni, A Medrano, G. A., Friedland, C and De Micheli, A Effect of intra venous infusion of potassi m-glucose-insulin sol tion on the electrocardiographic signs of myocardial infarction Am. J Cardiol. 9 166, 1962.

Experimental and laboratory reports

The use of single plane angiocardiograms for the calculation of left ventricular volume in man

Harold Sandler M.D
*Harold T Dodge M D***
Seattle Wash

Biplane angiocardiography has been used by various investigators for calculating left ventricular volume (LVV) and volume changes in man.[1-14] These calculations were based on the assumption that the left ventricular (LV) chamber can be represented by an ellipsoid reference figure. It will be the purpose of this report to show that measurements from biplane films demonstrate that the LV chamber can be represented by an ellipsoid of revolution reference figure (prolate spheroid). It will then be demonstrated that quantitative calculations of LVV and changes in volume can be made from serial angiocardiograms taken in a single plane (anteroposterior) projection.

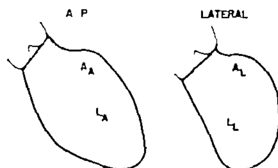
Material

The material used in this study was obtained from 55 patients with heart disease of varied etiologies. 48 of these had pure or mixed mitral and/or aortic valvular heart disease, 4 had idiopathic large hearts, 2 had subvalvular aortic stenosis and 1 had arteriosclerotic heart disease. All subjects are studied in the postabsorptive state without premedication. Biplane films were recorded by a Schonander film changer in the anteroposterior (A P) and left lateral projections. Six films per second were obtained in all but four subjects in whom 12 films per second were obtained. A total of 34 subjects were studied by selective injections of 50 to 75 c.c. of 75 per cent sodium diatrizoate (Hypaque) into the left atrium, 21 subjects by injections directly into the left ventricle. Only data from subjects in whom the margins of the LV chamber could be sharply delineated on films taken in the two projections were included in this study.

Methods and results

A total of 1,204 paired observations of LV dimensions were obtained during the cardiac cycle from biplane angiocardiograms taken in the A P and lateral projections in 55 subjects with heart disease of varied etiologies. Since it is the purpose of this study to evaluate a method for calculating LVV from measurements on films taken in a single A P projection, the results will be presented in the following steps: (1) LV chamber radii as calculated

From the Department of Medicine, University of Washington School of Medicine, Seattle Veterans Administration Hospital, Seattle, Wash.
This work was supported in part by Grant No. HE-01391-08, United States Public Health Service.
Received for publication March 10, 1967.
*Address: Medical Officer, Biomedical Research Branch, National Aeronautics and Space Administration, Ames Research Center, Moffett Field, Calif.
**Director, Division of Cardiology, University of Alabama School of Medicine, Birmingham, Ala.



MARGINS TRACED AREA PLANIMETERED

$D_A = \frac{4A_A}{\pi L_A}$ $D_L = \frac{4A_L}{\pi L_L}$

$L_M = L_A$ OR L_L WHICHEVER LARGEST

$V = \frac{\pi}{6}(D_A\ D_L\ L_M)$

Fig. 1. Area-length method.

from the films taken in the A-P and lateral projections, will be compared. Knowledge of this relationship between chamber radii will allow A-P chamber radius to be substituted for lateral chamber radius in order to calculate LV volume from a single A-P projection. (2) LV spatial position and change in position during the heart cycle will be calculated from the measurements used to determine LV spatial length. The magnitude of foreshortening of chamber length on A-P films due to front-to-back tilt of the LV chamber will be assessed by these calculations at end-diastole and the extent to which this change occurred during the cardiac cycle. A comparison will be made of the maximal length of the LV image measured on A-P films and the calculated spatial apex-to-aortic

$\frac{D_L}{2} = .987\frac{D_A}{2} + .10$

$S_{Y \cdot X} = .24$ cm

$r = .930$

1204 OBSERVATIONS

LATERAL RADIUS $D_L/2$ cm

A-P RADIUS $D_A/2$ cm

Fig. 2. Comparison of A-P and lateral chamber radii.

valve distance which represents the true long axis of the LV chamber The magnitude of variation between these variables will be used as a *means* to determine whether LV maximal length on A P films can be used to represent the major axis of the ellipsoid reference figure used to calculate LVV (3) Volumes calculated from data on biplane films will be compared with volumes calculated from the same films using data only on A P films. It will be important to determine whether these values are linearly related (4) Stroke volume calculated from appropriate biplane films, as described above will be compared to stroke volume calculated from identical films using data on A P films. This comparison will be used to determine whether the difference of end diastolic and end-systolic volumes, calculated from A P films, is related to the same volume differences (stroke volume) calculated from biplane films even though the absolute values of volumes calculated by each method may differ significantly

Comparison of A P and lateral chamber dii A P and lateral chamber radii were calculated for each set of biplane films as illustrated in Fig 1 All measurements were corrected for nonparallel x ray beam distortion by a mean correction factor derived from the estimated center of mass of the LV chamber The margins of the projected LV image were traced and each respective radius $\left(\frac{D}{2}\right)$ was calculated as

$$\frac{D}{2} = \frac{2A}{\pi L_M} \qquad (1)$$

where A = respective plan metered area of LV image and L_M = its respective longest measured length Fig 2 illustrates the comparison of 1,204 observations of chamber radii for the 55 patients included in this study using the UCLA BIMED 02D computer program on an IBM 7090-7094 computer A close linear relationship was demonstrated between A P radius $\left(\frac{D}{2}\right)$ and lateral radius $\left(\frac{D}{2}\right)$

$$\frac{D}{2} = 0.98\ \frac{D}{} + 0.10$$

$$s_{y.x} = 0.24\ cm.,\ = 0.930 \qquad (2)$$

Equation (2) demonstrates that A P chamber radius was equal to, or slightly exceeded lateral chamber radius in the majority of the subjects included in this study In 15 subjects, $\frac{D_A}{2}$ was found to slightly and regularly exceed $\frac{D_L}{2}$ during the heart cycle.

A comparison between maximal chamber length on A P films (L_A) and spatial chamber length (ρ) The true long or major axis of the left ventricle is the distance from the apex to the aortic valves. Since the left ventricle does not usually lie parallel to either of the biplane films, projections of the major axis of the chamber on either the A P or lateral films will be shorter than its actual or spatial length In order to quantitatively determine LV length it is necessary to construct a triaxial reference figure for the x ray equipment. The point of intersection of the central beams of the x ray tubes is used as the origin for this reference system. Since the patient lies on his back before the biplane changer frontal plane (X Y) projections occur on A P films, sagittal (X Z) projections occur on the lateral films. Any point which can be simultaneously identified on a set of films can be given a precise spatial location. Before such points can be located spatially however they must be corrected for geometric distortion due to nonparallel x ray beams. The techniques used for this correction have been previously published Fig 3 schematically illustrates a set of

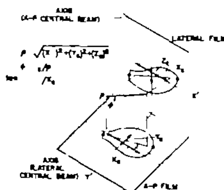


Fig 3 Calculation of spatial length.

films at end-diastole. The projections of the reference X, Y, and Z axes are constructed on each film. The corrected positions of the apex and aortic valves are also shown on each film. The spatial apex-to-aortic valve length of the LV chamber (ρ) is then calculated as

$$\rho = \sqrt{(X)^2 + (Y)^2 + (Z)^2} \qquad (3)$$

where X, Y_m, Z represent component lengths directly measured from each set of films as illustrated in Fig. 3.

In order to test the assumption that the longest measured length on the AP films (L_A) represented a measure of the major axis of the reference prolate spheroid, L_A was compared to ρ during the heart cycle. It should be noted that L_A does not represent the frontal plane projection of the spatial apex to aortic valve length as can be seen in Fig. 1. ρ and L_A were demonstrated to be linearly related:

$$L_A = 0.98\,\rho - 0.02 \quad S_{y.x} = 0.42\ cm$$
$$r = 0.957 \quad N = 842 \qquad (4)$$

In almost all subjects a difference was regularly seen between values of L_A and ρ throughout the heart cycle with L_A being less than or equal to ρ due to foreshortening of the projected major axis of the LV chamber by the front-to-back tilt of heart position within the chest. A comparison between ρ and L_A at end-diastole is included in Table I. Calculations of LV spatial position (presented below) demonstrated that LV spatial length at end-diastole lies nearly parallel to the frontal plane, the AP plane projection of this length will therefore closely approximate the true spatial length. L_A is also measured across an additional area (½ of the aortic cross-sectional diameter) which is not included in the measurement of spatial length. This additional distance tends to compensate for the foreshortening of the projected long axis of the left ventricle due to its position in the chest or in some instances even causes L_A to exceed calculated values for ρ. In 43 subjects the longest measured length of the LV chamber could be regularly measured on the AP films. In six subjects the longest measured length of the LV chamber was regularly measured on the lateral films and in six additional subjects the maximal length of the chamber was measured in the lateral films in the majority of recorded films. These latter subjects are starred in Table I and invariably have the most severe front-to-back tilt in heart position within the chest.

Spatial position and movement of the LV chamber during the heart cycle. LV position within the chest and the magnitude of movement of the chamber during the cardiac cycle are important parameters in predicting the error of using measurements from AP films to calculate LV volume and change in volume. A marked front-to-back tilt at end-diastole or a marked front-to-back (Z axis) movement during the heart cycle would foreshorten the recorded image of the LV chamber on AP films. These changes were quantitatively assessed by determining the spatial angle ϕ (spherical coordinator) which is made by the spatial length of the LV chamber (ρ) and the Z axis, and by the change in ϕ during the cardiac cycle. ϕ is defined as

$$\phi = \sin\left(\frac{Z}{\rho}\right) \qquad (5)$$

where Z = measured component of ρ on the Z axis. These relationships are illustrated in Fig. 3.

ϕ as determined by equation (5) represents the angle between LV spatial length and the AP plane. All values for ϕ calculated at end-diastole are listed in Table I and varied from 62 degrees (subject J. K. K.) to 3 degrees (subject S. S.). The mean value for ϕ at end-diastole was 20.3 degrees ± 9.7 degrees. Front-to-back changes in chamber position from end-diastole to end-systole are designated as $\Delta\phi$ and are also listed in Table I. These changes are determined throughout the heart cycle from a composite plot of all calculated values for ϕ as illustrated in Fig. 4. The mean absolute front-to-back change in heart position during the cardiac cycle was 3.8 degrees ± 1.6 degrees. The angle between ρ and the AP films was noted to decrease during systole in 26 subjects (range of decrease −1 degree to −9 degrees) which essentially represented

Table I

No.	Patient	Diagnosis	END DIASTOLIC DIMENSIONS, cm $D_A/2$	$D_L/2$	$L_A/2$	$L_M/2$	$\ell/2$	VOLUME, cc EDV*	EDV**	SV*	SV**	SV***	POSITION, deg φ	Δφ	θ	Δθ
1		TS MS AS	2.56	2.56	4.82	4.82	4.90	121	134	88	90	86	15	2	—	—
2	LBB	MS	2.48	49	5.07	5.07	—	118	131	68	72	69	—	—	—	—
3	EBB	MS,AI,MI	2.80	2.67	4.56	4.64	5.00	122	129	69	66	63	31	+4	29	+6
4	HBB	MS,MI	2.95	3.1	37	5.37	5.82	183	196	114	108	101	21	+5	46	+6
5	FBB	AS	3.28	3.38	6.20	6.20	6.09	263	279	79	78	74	18	+2	—	—
6	CBB	MS,MI	2.40	2.70	4.64	4.64	4.45	124	134	70	73	69	18	+4	—	—
7	EBB	MS MI	3.14	3.19	5.71	5.71**	5.84	219	236	149	155	148	19	+1	—	—
	RCC	MI,MS	3.18	3.24	4.89	4.89	5.06	192	207	120	117	111	24	+1	37	+2
9	OCC	MS,AI,MI	3.02	13	6.13	6.13	6.44	221	234	68	68	64	20	+2	—	—
10	WCC	AI	3.10	3.54	5.28	5.28	5.63	221	213	133	132	127	—	—	—	—
11	BCC	MS,AI	3.88	3.88	6.32	6.32	6.12	348	358	249	261	245	13	+4	48	+3
12	JD	AI	77	43	6.65	6.65	6.37	331	396	205	238	217	12	+4	45	+5
13	WD	RHEPOND AI	3.04	3.53	5.72	5.72	5.70	235	222	13	135	119	26	+4	51	+8
14	WE	AS AI	3.10	3.16	5.76	5.76	6.82	21	232	91	91	86	17		—	—
15	EE	MS,AI	2.68	2.71	47	78**	4.74	131	141	88	84	79	23	−4	—	—
16	BBB	SAVS	2.66	2.92	6.38	6.38	6.38	190	192	143	164	146	17	−3	49	+4
17	BBG	AI MI,MS	3.21	3.17	6.79	6.79	6.45	264	293	120	122	116	17	+5	41	+7
18	VBG	MS,MI	2.48	2.29	4.63	4.53	4.64	96	117	63	75	71	20	+3	28	+7
19	FDB	MS AI	08	3.06	5.19	5.19	5.10	186	206	89	100	95	20		28	+8
20	KGB	MS,MI	2.64	2.74	5.31	5.3	6.00	146	162	85	81	77	7	+4	53	+6
21	CH	MAH	3.05	2.80	4.45	5.33*	5.25	173	174	127	122	115	40	+7	50	+9
22	CH	AI	3.83	4.00	5.79	5.79	5.99	341	356	206	228	218	7	3	—	—
23	VHH	MI,MS	18	24	5.39	5.39	5.55	210	224	141	148	141	20	+4	31	+7
24	WH	AI	96	4.16	6.15	18	—	399	402	181	190	182	—	—	—	—
25	JHH	AI AS	3.51	4.13	5.27	5.27	5.80	293	272	212	213	201	35	−3	—	—
26	OHH	MAH	3.53	3.85	76	5.76	21	301	300	85	95	62	11	+4	54	+3
27	RKK	AS,AI	3.80	3.12	19	6.19	6.16	280	282	170	192	183	1	5	—	—
28	JKK	MS,AI	3.09	13	5.06	5.06	6.16	186	202	88	9	87	25	2	42	+5
29	JKK	AI,MS MI	3.44	3.04	4.85	5.42*	06	216	240	160	167	159	62	+3	30	+8
30	MLL	IHH,MI	0	28	5.44	5.44	6.26	365	352	97	108	98	1	+6	39	+7
	CMM	AI	3.88	4.34	7.00	7.00	6.69	482	437	205	207	197	14	−	—	—
32	JMM	MI SBE	2.30	2 1	5.25	5.25	5.64	114	116	58	54	51	26	+3	29	+3
33	RMM	SAVS	2.38	2.03	90	93*	00	110	114	79	87	83	24	+5	33	+7
34	GM	MI,MS,AS,AI	2.92	2.63	5.63	5.63	6.05	144	201	84	108	98	10	8	—	—
35	WN	AI,AS	84	3.77	5.16	5.16	5.69	264	271	151	172	164	—	—	—	—
36	CR	AI,AS	3.84	4.04	35	6.30	6.21	379	392	128	130	114	9	+5	43	+2
37	DO	AI,AS	3.14	3.10	64	1	6.26	192	192	139	130	124	30	+4	32	+9
38	JP	MI	4.82	4.98	6.15	15	—	738	796	201	185	179	—	—	—	—
39	ARR	AS	3.09	26	5.87	5.87	6.05	226	235	138	146	139	20	2	48	+4
40	WR	AI AS	2.82	3.11	6.34	6.34	6.80	233	212	142	146	139	21		—	—
41	AR	AS,AI	3.16	3.17	6.67	6.67	6.45	281	273	98	98	100	12	+4	—	—
42	JS	MI MS	2.82	2.70	4.90	4.90	4.65	141	165	80	87	82	7	−5	—	—
43	CSS	MS MI,AI	3.65	3.18	5.93	5.93	5.68	257	313	119	138	128	18	+9	43	+6
44	SS	MI,MS	2.43	2.82	94	4.94	71	119	122	48	60	66	3	+2	43	+8
45	VS	MS	2.25	2.39	4.43	43	.36	89	84	51	52	50	20	7	25	+8
46	DT	MS MI	3.10	3.06	07	5.07*	4.74	168	185	108	123	117	3	+8	30	+ 0
47	ATT	MS MI	2.48	2.93	49	49	66	123	11	62	63	60	21	+6	49	+7
48	ST	AI,AS	3.64	3.67	6.48	6.48	5.65	29	304	26	33	31	24	+6	—	—
49	FVY	AS	2.79	2.67	4.28	43*	4.72	134	40	7	45	47	28	1	35	+8
50	BW	AS,AI	3.12	3.3	5.85	5.85**	6.12	237	240	94	93	88	26	+	35	+5
51	EW	AS,AI	2.80	2.84	5.05	5.61	5.61	63	43	107	89	90	37	3	31	+12
52	JW	3 HB	3.10	3	4.80	4.80	4.85	70	185	100	10	96	29	−4	63	+8
53	MW	MS MI AI	2.84	2.86	31	4.31	4.18	132	46	72	74	80	20	+5	35	+8
54	CW	MS MI	2.91	2.5	6.29	6.29	5.79	201	220	116	122	116	12	+4	—	—
55	FW	MS AI,MI,TS	2.43	67	5.86	5.86	5.48	168	170	87	86	82	10	+2	4	+2
MEAN													20.3	3.8	39.8	6.2
STANDARD DEVIATION													7	1.6	6.6	2.5

AS, aortic stenosis; AI, aortic insufficiency; MS, mitral stenosis; MI, mitral insufficiency; SAVS, subaortic stenosis; TS, tricuspid stenosis; IHSS, idiopathic hypertrophic subaortic stenosis.

$\frac{D_A}{2}$, $\frac{D_L}{2}$, respectively, A-P and lateral chamber radii; $\frac{L_A}{2}$, maximal measured chamber semi-axis on A-P films; $\frac{L_M}{2}$, maximal measured chamber semi-axis whether A-P or lateral film; $\frac{\ell}{2}$, ½ spatial apex to aortic valve length; EDV*, end-diastolic volume calculated by equation (6) and adjusted by equation (7), c.c.; EDV**, end-diastolic volume calculated by equation (8), c.c.; SV*, stroke volume calculated from adjusted biplane volumes, c.c.; SV**, stroke volume calculated from only A-P films; SV***, stroke volume calculated from only A-P films and adjusted by equation (9), c.c.; φ, angle between spatial length and plane A-P films; θ, angle between spatial length and plane of lateral films.

*Lateral film length greater than A-P length throughout cardiac cycle.

**Lateral length greater than A-P length for majority of films.

a movement of the apex away from the anterior chest wall in these cases. Any difference or error between L and ℓ on end-systolic films would be less than on films taken at end-diastole in these cases, since the chamber has moved to a position which is more nearly parallel with the A-P films. In 14 subjects, the apex moved forward (toward the anterior wall). This movement occurred early in systole (increasing the angle between ℓ and A-P films) followed by a backward

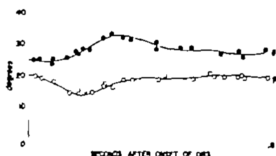


Fig. 4. Angular movement of spatial length. ● Angle between spatial length and lateral film. o, Angle between spatial length and A-P film. Subject E. S.

in mid and late systole. These subjects are indicated by plus-minus values in Table I. In eight of these latter 14 subjects the predominant movement was to decrease the spatial angle made with the A-P plane at end-systole (decrease of –? degrees to –5 degrees); in three subjects the forward and backward movements were of equal magnitude (range 1 degree to 3 degrees) and in three subjects, the angle increased at end-systole (range of increase 1 degree to 5 degrees). In ten subjects the heart (apex of the left ventricle) moved toward the anterior chest wall during systole; the angle between ρ and the A-P films increased from 2 degrees to 5 degrees at end-systole in these cases. It was concluded from these calculations, that a projection of LV spatial length is slightly foreshortened on A-P films; however, measurements of maximal image length on the A-P films closely agree with calculated spatial length for all subjects. Furthermore, chamber motion during the cardiac cycle is small and is not a source for significant error in the measurement of LV chamber length on A-P films. In fact, for the majority of subjects in this study, the LV chamber came to lie more parallel with the A-P plane at end-systole than at end-diastole.

Comparison of volume calculated from biplane films (V'') and volumes calculated from data on A-P films (V_{A-P}). LV volumes (V) were calculated from biplane films by the area-length method as illustrated in Fig. 1, using the volume formula of an ellipsoid

$$V = \frac{4}{3}\pi \cdot D_A/2 \times D_L/2 \times L_M/2 \quad (6)$$

where $D_A/2$ and $D_L/2$ are the respective A-P and lateral chamber radii calculated by equation (1) and L_M the longest measured chamber length whether on the A-P or lateral film. Earlier studies of post-mortem hearts demonstrated that volumes calculated by this technique, as well as all other tested methods, exceeded known volumes of the LV chamber.[8] These studies, however, demonstrated a linear relationship between known volumes (V') and volumes (V) calculated by the area-length method so that

$$V' = 0.928 V - 3.8 \quad S_{Y \cdot X} = 8.2 \text{ c.c.} \quad (7)$$

This equation was used to adjust or correct all volumes calculated by the area-length method in this study.

The observations of equation (2) which demonstrated a close relationship between transverse chamber radii and equation (4) which demonstrated a close relationship between ρ and L, suggested that it might be possible to determine LV volume from films taken in a single A-P projection. Therefore $\frac{D_A}{2}$ was substituted for $\frac{D_L}{2}$ and $\frac{L}{2}$ substituted for $\frac{L_M}{2}$ in equation (6). LVV from data on A-P films (V_{A-P}) was then calculated as

$$V_{A-P} = \frac{4}{3}\pi \times \left[\frac{D_A}{2}\right]^2 \times \frac{L}{2} \quad (8)$$

All measurements from A-P films were corrected for nonparallel x-ray beam distortion by the correction factor determined for the A-P plane during biplane filming. Volumes (V_{A-P}) calculated by equation (8) were compared to volumes (V'') calculated by equation (6) and adjusted by equation (7). This comparison demonstrated that

$$V'' = 0.951 V_{A-P} - 3.0 \quad S_{Y \cdot X} = 15.0 \text{ c.c.}$$
$$r = 0.990 \quad N = 1,204 \quad (9)$$

The results using the UCLA BIMED 02D program on an IBM 7090-7094 computer are illustrated in Fig. 5. Single plane end-diastolic volumes as listed in Table I exceeded biplane end-diastolic volumes

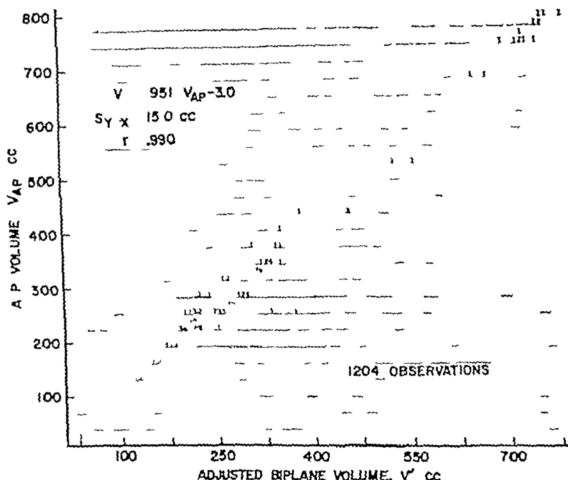


Fig. 5 Comparison of single plane and biplane volumes.

for 46 subjects. In nine of these 46 subjects, the difference between single plane and biplane volumes was greater than 20 c.c. (range 25 to 65 c.c.) After correction of V_{AP} by equation (9) the overestimate of volume in these nine subjects was corrected to a mean value of 13 5 c.c. representing an average error of 5 per cent (range 0 4 to 14.8 per cent) In nine additional subjects, single plane end-diastolic volumes were less than calculated biplane values. The mean underestimation of ventricular volume in this group after correction by equation (9) was 4 8 c.c., representing an average error of 9 0 per cent (range 5.2 to 18 4 per cent) The major cause for underestimation of volume in this latter group was due to differences in calculated values for transverse chamber diameters, where calculated values of D_L exceeded calculated values of D_A. In only one subject (E. W.) in whom there was a significant overestimate or underestimate of volume did the maximal chamber length occur on the lateral films. The largest per cent error for adjusted calculated volume by single plane techniques occurred in this subject and was an underestimation of volume. These analyses demonstrate that LVV calculated by this single plane technique are closely and linearly related to volumes calculated by the biplane technique.

Comparison of LV stroke volume determined from biplane films (SV') and single plane film (SV'''). It has already been pointed out that the calculation or measurement of left ventricle dimensions from x rays taken in a single plane may be modified by heart position or changes in

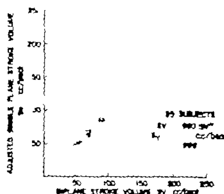


Fig 6 Comparison of single plane and biplane stroke volumes

heart position or configuration during the cardiac cycle In order to assess whether the changes in ventricular dimensions used to calculate end-diastole volume and end systolic volume from A P films were linearly related to the changes in the same respective dimensions determined from measurements on biplane films LV stroke volumes were calculated by each technique and compared to one another

Volumes calculated for each set of biplane films and adjusted by equation (7) were plotted with respect to the time of the cardiac cycle to construct a composite LV volume curve for the 3 to 5 heartbeats during angiocardiography LV stroke volume (SV) was calculated as the difference between end-diastolic and end-systolic volumes Each value for end-diastolic or end systolic volume used in this part of the study represented the mean of at least 2 to 4 volume observations respectively

LV stroke volume from data only on A P films (SV) was calculated using equation (8) in an identical manner and for the same films used to calculate SV A comparison between the two methods demonstrated a consistent and linear overestimation of stroke volume by unadjusted single plane calculations.

$$SV = 0.935\ SV + 3.2 \quad N = 55$$

$$r = 0.988 \quad S_{Y \cdot X} = 7.5\ c.c\ beat \qquad (10)$$

It is of interest that the regression coefficient of equation (10) is very similar to that of equation (3) which was used to adjust biplane volumes before calculating SV When each of the respective volumes used to calculate SV was adjusted by equation (9) and used to derive an adjusted single plane stroke volume (SV) a close and linear relationship was demonstrated between SV and SV The comparison between SV and SV is listed in Table I and illustrated in Fig 6 and demonstrated that

$$SV = 0.980\ SV + 3.7 \quad N = 55$$

$$r = 0.988 \quad S_{Y \cdot X} = 7.8\ c.c./beat \qquad (11)$$

In this latter group stroke volume was calculated to be equal by the two methods in five subjects and was 5 c.c./beat greater or less than the other method in 25 subjects. Single plane stroke volume overestimated biplane stroke volume by 6 to 14 c.c. beat in ten subjects and underestimated it by 6 to 22 c.c./beat in 15 subjects. The mean percentage error for the group as a whole was 6.7 per cent.

Discussion

The use of biplane films for the calculation of LVV and volume change is based on the use of an ellipsoid reference figure The accuracy of this assumption has been tested by studies in postmortem hearts filled with barium sulfate paste by casts of the LV chamber at postmortem examinations, by models of the LV chamber and by a comparison of stroke volume determined from biplane angiocardiographic films with stroke volume determined by Fick or dye dilution techniques in subjects without clinical evidence of valvular insufficiency These comparisons have shown biplane angiocardiographic techniques to be a quantitative method for calculating LVV and volume change

The data in this study have demonstrated that the respective minor diameters of the LV chamber do not differ significantly from one another and more importantly are linearly related This suggested that a prolate spheroid could be reasonably substituted as the reference figure for calculating LVV and volume change The A P plane projection was chosen for use in calculations of volumes after calculations demonstrated that the long axis of the LV could be measured in the majority of subjects on the A P films and compared favorably with the calcu

lated spatial length of the LV chamber. Others[4] have suggested the use of the right anterior oblique (RAO) rather than the A-P projection for calculating LV chamber volumes from films taken in a single projection. The RAO projection seems ideally suited for calculation of volume since it compensates for the foreshortening of spatial LV length due to the position of the heart within the chest. However, studies of maximal image length on the A-P films and calculated chamber spatial length showed a close linear relationship. Studies of the movement of the LV chamber during the cardiac cycle also demonstrated that significant front-to-back movements do not occur with systole and that twice as much angular movement occurred in the head-to-foot direction (see Figs. and 3 and angle θ listed in Table I) than in the front-to-back direction (angle φ). These latter changes may lead to a foreshortening of the long axis of the chamber during systole on RAO projected films and lead to an error in calculated end-systolic volume, whereas there is little change in the angle of the LV in the A-P projection that would influence calculation of stroke volume. Furthermore, the reproducibility of a RAO position is difficult from subject to subject or in the same subject without the use of special equipment or time-consuming measurements. A comparison of A-P and RAO projections for calculation of LVV in heart models is presently in progress in this laboratory.

Calculations of LVV from biplane films using equation (2) regularly overestimated known volumes in postmortem hearts regardless of the methods used for volume calculation. The reasons for overestimates of volume by biplane films has been discussed and may best be explained by the fact that a smooth surfaced ellipse is used to represent the irregular cavity of the LV chamber. Equation (3) represents the correction for these observed differences. LVV calculated from data in a single plane compared favorably and closely with unadjusted or uncorrected volumes calculated from biplane films. Single plane volumes also exceeded or equalled adjusted or corrected biplane volumes for 49 of the 55 patients included in this study. On the basis of these studies, it appears that quantitative calculations of ventricular volume and stroke volume can be made from films taken in a single plane. Present biplane equipment is costly and is capable of filming rates of six films per second and occasionally 12 films per second. These rates of filming do not permit beat-to-beat analysis of the details of ventricular volume curves, but require construction of composite curves to obtain volume data for the entire cardiac cycle. The present studies suggest that LVV and change in volume can be determined from cineangiocardiographic studies taken in a single plane. Filming is now available during cineangiocardiographic studies at rates of 30 to 60 frames per second and studies up to 524 frames per second have also been reported. These rapid rates of filming will make it possible to determine much more detailed volume curves and to follow volume change from beat-to-beat in those cycles in which there is sufficiently adequate visualization of the LV chamber to accurately delineate chamber margins.

Cineangiocardiographic methods have been used to determine LVV by several investigators. The application of these techniques for volume studies in man presents a number of technical problems which include correction for image distortion, the need for LV injections of contrast material in order to obtain adequate resolution and image definition to permit single frame analysis during the cardiac cycle, and the reduction of a large amount of volumetric data. Methods for digital computer processing of the data resulting from cineangiocardiographic studies is presently under investigation in our laboratories.

Summary

A method has been presented for calculating LVV from films taken in a single (A-P) plane projection. This method is based on the assumption that the LV chamber can be represented by an ellipsoid of revolution (prolate spheroid) reference figure. LV volumes were calculated from measurement made on biplane films taken in the A-P and left lateral heart projections. The biplane studies demonstrated that the A-P and lateral diameters of the ventricular chamber were very

closely related. Volumes calculated from measurements made only on A P films closely agreed with biplane calculations of volume. The use of single plane techniques did not result in significant errors for the calculation of absolute end-systolic volume or for calculation of stroke volume.

REFERENCES

1. Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. J.: Use of biplane cinefluorography for measurement of ventricular volume, Circulation 18:1105, 1958.
2. Arvidsson, H.: Angiocardiographic determination of left ventricular volume, Acta radiol. 56:321, 1961.
3. Dodge, H. T., Sandler, H., Ballew, D. W., and Lord, J. D., Jr.: Use of biplane angiocardiography for the measurement of left ventricular volume in man, Am. Heart J. 60:762, 1960.
4. Arvidsson, H.: Angiocardiographic observations in mitral valvular disease, with special reference to the volume variation in the left atrium, Acta radiol. (Suppl. 158), 1958.
5. Davila, J. C., and Sanmarco, M. E.: An analysis of the fit of mathematical models applicable to the measurement of left ventricular volume, Am. J. Cardiol. 18:31, 1966.
6. Dodge, H. T., Hay, R. E., and Sandler, H.: A angiocardiographic method for directly determining left ventricular stroke volume in man, Circulation Res. 11:739, 1962.
7. Carlisle, R., Grant, C., Bunnell, I., and Greene, D. G.: Pressure volume loops of the human left ventricle from one plane cineangiograms, Clin. Res. 12:440, 1964.
8. Greene, D. G., Carlisle, R., Grant, C., and Bunnell, I. L.: Estimation of left ventricular volume by one-plane cineangiography, Circulation 35:61, 1967.
9. Moore, D.: Simple assessment of left ventricular function during cardiac catheterization in children, Circulation, 32(Suppl. 2):153, 1965.
10. Gimenez, J. L., Stewart, G. H., Lynch, P. R., and Stauffer, H.: Biplane high-speed (540 frames per second) cinefluoroscopy. Preliminary observations (Abstr.), in 5th Rochester Symposium on Cineradiology, University of Rochester, Rochester, New York, March 3 to 5, 1966.
11. Gribbe, P., Hirvonen, L., Lind, J., and Wegelius, C.: Cineangiocardiographic recordings of the cyclic changes in volume of the left ventricle, Cardiologia 34:348, 1959.
12. Cohn, K., Sandler, H., and Hancock, E. W.: The mechanism of pulsus alternans, Clin. Res. 15:92, 1967.
13. Chapman, C. B., Baker, O., Mitchell, J. H., and Collier, R. C.: Experiences with a cinefluorographic method for measuring ventricular volume, Am. J. Cardiol. 18:25, 1966.
14. Lynch, P. R., Stauffer, H., and Peterson, K.: Assessment of impaired ventricular ejection by precision analysis of 270 fps cinefluoroscopy (Abstr.), in 4th Rochester Symposium on Cineradiology, University of Rochester, Rochester, New York, Nov. 15 to 16, 1963.
15. Ohlsson, N.: Left heart and aortic blood flow in the dog. Precision motion analysis of high speed (270 frames/sec) cinefluorographic recordings, Acta radiol. (Suppl. 213), 1962.

New quantitative vectorcardiographic criteria for the detection of unsuspected myocardial infarction in diabetics

Ronald H. Selvester, M.D.
Herbert B. Rubin, M.D.
J. Andrew Hamlin, M.D.
William W. Pote, M.D.
Los Angeles, Calif.

The difficulty of establishing the diagnosis of myocardial infarction in the diabetic patient is well known. In a study of autopsy proved large myocardial infarcts, Rubin and Weiss[2] found that the electrocardiogram (ECG) was considerably less accurate in the diagnosis of myocardial infarction in the diabetic than in the nondiabetic patient. From these data and from the well-controlled series of Woods, Laurie and Smith and Johnson, Achor, Burchell and Edwards[4] it is clear that conventional ECG criteria diagnose definite infarction in nondiabetic subjects with about 50 to 60 per cent accuracy and in diabetic patients with about 30 to 40 per cent accuracy.

The complications observed in patients with diabetes mellitus are largely due to the vascular changes that occur in this disease. Seventy per cent of all deaths among diabetic patients in the United States are due to vascular disease. Though the incidence of diabetes in the general population is 1 to per cent the record of patients with myocardial infarction indicate that between 10 and 20 per cent are diabetic.[9,1] Necropsy examination reveals that coronary artery occlusion occurs in the diabetic group about five times as frequently as in the nondiabetic group,[11] and that in older diabetic persons, in whom the onset occurred after the age of 40, severe coronary arteriosclerosis occurs almost universally.[12] It is not uncommon to find scars of old infarcts at autopsy of diabetic patients who died of other causes without a history of myocardial infarction.[1] Furthermore, it has been observed that in older diabetic patients the incidence of myocardial infarction is unrelated to the duration or the degree of control of the diabetes.[13,14] Consequently, in older patients, by the time a diagnosis of diabetes is made clinically, one can expect that severe coronary artery disease and ischemic fibrosis and or infarction of the myocardium has occurred.

Vectorcardiographic criteria for myocardial infarction have been described by

From the Medical Science Service, Rancho Los Amigos Hospital, Downey, the Cardiopulmonary Laboratory at White Memorial Hospital, Los Angeles, and the Department of Internal Medicine, Loma Linda University at Los Angeles, Calif.

This investigation was supported in part by grants in aid from the Los Angeles County Heart Association and the Imperial County Heart Association, and United States Public Health Service Research Grant No. HE 10723-01.
Received for publication April 26, 196

closely related. Volumes calculated from measurements made only on A-P films closely agreed with biplane calculations of volume. The use of single plane techniques did not result in significant errors for the calculation of absolute end-systolic volume or for calculation of stroke volume.

REFERENCES

1. Chapman, C. B., Baker, O., Reynolds, J., and Bonte, F. J.: Use of biplane cinefluorography for measurement of ventricular volume, Circulation 18:1105, 1958.
2. Arvidsson, H.: Angiocardiographic determination of left ventricular volume, Acta radiol. 56:321, 1961.
3. Dodge, H. T., Sandler, H., Ballew, D. W., and Lord, J. D., Jr.: Use of biplane angiocardiography for the measurement of left ventricular volume in man, Am. Heart J. 60:762, 1960.
4. Arvidsson, H.: Angiocardiographic observations in mitral valve disease [illegible] special reference to the volume variations in the left atrium, Acta radiol. (Suppl. 158), 1958.
5. D[illegible] J. C., and Sannmarco, M. E.: Analysis of the fit of mathematical models applicable to the measurement of left ventricular volume, Am. J. Cardiol. 18:31, 1966.
6. Dodge, H. T., H[illegible], R. E., and Sandler, H.: A[illegible] angiocardiographic method for directly determining left ventricular stroke volume in man, Circulation Res. 11:739, 1962.

Carlisle, R., Grant, C., B[illegible]nell, J. [illegible] and Greene, D. G.: Pressure volume loops of the human left ventricle from one plane cineangiograms, Clin. Res. 12:440, 1964.

8. Greene, D. G., Carlisle, R., Grant, C., and Bunnell, I. L.: Estimation of left ventricular volume by one-plane cineangiography, Circulation 35:61, 1967.
9. Moor, D.: Simple assessment of left ventricular function during cardiac catheterization in children, Circulation 32(Suppl. 2):153, 1965.
10. Gimenez, J. L., Stewart, G. H., Lynch, P. R., and Stauffer, H.: Biplane high-speed (340 frames per second) cinefluoroscopy. Preliminary observations (Abstr.). In 5th Rochester Symposium on Cineradiology, University of Rochester, Rochester, New York, March 3 to 5, 1966.
11. Gribbe, P., Hirvonen, L., Lind, J., and Wegelius, C.: Cineangiocardiographic recordings of the cyclic changes in volume of the left ventricle, Cardiologia 34:348, 1959.
12. Cohn, K., Sandler, H., and Hancock, E. W.: The mechanism of pulsus alternans, Clin. Res. 15:92, 1967.
13. Chapman, C. B., Baker, O., Mitchell, J. H., and Collier, R. C.: Experiences with a cinefluorographic method for measuring ventricular volume, Am. J. Cardiol. 18:25, 1966.
14. Lynch, P. R., Stauffer, H., and Peterson, K.: Assessment of impaired ventricular ejection by precision analysis of 270 fps cinefluoroscopy (Abstr.). [illegible] 4th Rochester Symposium on Cineradiology, University of Rochester, Rochester, New York, Nov. 15 to 16, 1963.
15. Ohlsson, N.: Left heart and aortic blood flow in the dog. Precision motion analysis of high speed (270 frames/sec) cinefluorographic recordings, Acta radiol. (Suppl. 213), 1962.

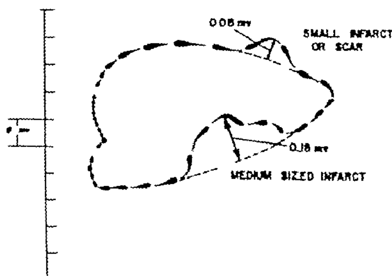


Fig 1 A medium-sized and small nfarct by the criteria proposed is show n on horizontal plane cube ectorcardiogram The medium-sized nfarct show the displacement f om smoothly transcribed loop of 0 18 mv maximum magnitude for dur tion of 10 msec The small infarct show displacement of 0 08 mv for 4 msec.

Table II V C G criteria f nfarction*

Degree	M gnitude		Duration (msec)
	Child (< 10) (mv)	Adult (> 10) (mv)	
Normal	0 06 or less	0 04 or less	
Possible	0 07–0 09	0 05–0 06	
Small	0 10–0 20	0 07–0 14	2-6
Medium	0 21–0.30	0 15–0 21	7 14
Large	0 31 or more	0 22 or mor	15 or more

*The abnormalit had to meet the above criteria either in magnitude or duration to be called abnormal to hat degree (see text)

The criteria thus established were based on a voltage alteration of sufficient dura tion or extent to distort the smooth pro g ession of the vectorcardiographic loop beyond that seen n the series of normal t acings. These criteria a described in Table II Examination of the normal series ndicated that there was greater voltage variation in any one segment of the tracing consistent with normalcy in the indi viduals under ten yea of age than there was in tl ose older than ten years The voltage criteria therefore varies witl the patient s age We have also classified the size of the lesions as small med um or large depending on the extent of voltage change or the time du ation over which the change occurred (Table II) The large lesions by these criteria correspond to the classical criteria for larger infarctions de scribed by various authors [11] and repre sent a large d splacement from a smooth loop or from an average loop for that age group

Based on vectorcardiographic changes, we also classified these lesions as to location into the follow ng areas (1) anteroseptal lower half (2) basal septal (3) apex or lateral, (4) free ventricular wall, posterior (5) superior including basal left ventricle, (6) free wall posterobasal and (7) inferior or diaph agmatic including basal left ventricle (F g) The vector changes of location were interpreted on the basis of th model of the VCC previously reported [8] This model assumes the human activation sequence to be sim lar to that reported by Scher and Young[22] and onfirmed in dogs l y ou group and more ecently confirmed in human subjects by Durrer and associates.[23]

The conventional 13-lead ECC were ead independently by th ee qualified ca diologists. They did not have the benefit

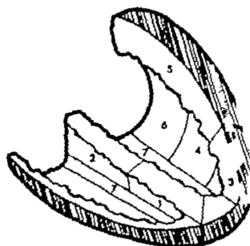


Fig. 2. An illustration of the subdivision of the heart into seven segments used for the purpose of location of infarction in this study.

of clinical history on any patient in the series, except for age, sex, and cardiac drugs.

The criteria used for selection of one interpretation from the three interpretations where there was a difference of opinion are found in Table III.

Results

Proposed vectorcardiographic criteria. In the examination of the VCG's of 106 people in the normal series, we found three patients who had changes in potential consistent with infarction by our criteria. These were men of ages 26, 45, and 47 at the time the tracings were done. In addition to these three, there were three others whose tracings fell into the questionable category.

Table III. Criteria for myocardial infarction

I. Definite myocardial infarction
   Two or more agreed
II. Possible myocardial infarction
   A. Two or more agreed
   B. One made the diagnosis of definite or possible myocardial infarction plus one or more diagnosed any of the following:
      1. Interventricular conduction defect
      2. Left axis deviation of minus 30° or more in the frontal plane
      3. Myocardial fibrosis
III. No evidence of infarction
   A. Normal ECG
      Two or more agreed, plus any diagnosis except definite myocardial infarction
   B. Possible normal ECG
      1. Two or more agreed
      2. One made the diagnosis of possible normal or borderline and the others a diagnosis including one of the following:
         a. Normal
         b. Incomplete right bundle branch block
            Questionable early hypertrophy
         d. Nonspecific ST-T change
   C. Interventricular conduction defect without other evidence of infarction
      1. Two or more had to agree on one of the following:
         a. Complete or incomplete right bundle branch block
         b. Complete or incomplete left bundle branch block
         c. Interventricular conduction defect type undetermined
   D. Left ventricular hypertrophy* without other evidence of infarction.
      Two or more had to agree
   E. Pulmonary disease without other evidence of infarction
      Two or more had to agree
   F. Nonspecific ST changes
      Two or more had to agree
   G. Digitalis effect
      Two or more had to agree

*There were no cases of right ventricular hypertrophy in this series.

When the criteria were applied to the nondiabetic random sample it was found that 11 of the 98 subjects had tracings indicative of infarction and one had a questionable abnormality. The ages of those showing an abnormality ranged from 25 to 73 years.

In the series of diabetic patients there were 32 with juvenile-onset diabetes (Table IV). Of these 14 had definite vectorcardiographic changes suggestive of small infarction and two others showed questionable abnormalities. In the maturity-onset group of 64 patients, 55 had vectorcardiographic evidence of infarction usually multiple, with an additional five patients demonstrating questionable changes. Thus, it was found that 44 per cent of the juvenile-onset diabetic group, and 94 per cent of the maturity-onset group, had tracings that were read as possible or definite infarction.

From Tables IV and V a comparison was made of evidence for infarction by the proposed vectorcardiographic criteria in juvenile-onset and maturity-onset diabetes as compared to the random group of comparable age. The χ^2 test indicated a significant increase in incidence of infarction ($p < 0.05$) in the total diabetic group. From Table IV a comparison was made of juvenile-onset with maturity-onset diabetes. The increased incidence of infarction in the maturity-onset group is significant ($p < 0.05$). This is confounded however by the difference in the ages of these two groups. An attempt was made to correct for the effect of aging by comparing each diabetic group to an age-comparable group from the random population and then evaluating the resultant differences, thus controlling for the effect of aging. A significant difference between juvenile-onset and maturity-onset groups *controlled for age was found* ($p < 0.05$). However the age distribution in the random group versus the diabetic group was not entirely comparable in each of these age groups (Table I). The age confounding therefore, between juvenile-onset and maturity-onset diabetes has not been entirely eliminated.

Table VI shows a comparison of the incidence of infarction compared to the duration of the diabetes and no relationship was observed. Table VI also shows the relationship between size of lesions as diagnosed by the VCG and the duration of the diabetes in both the juvenile-onset and maturity-onset groups. Again no relationship between size (severity of destructive disease) and duration was observed. However when the juvenile and maturity sets of data were combined and compared with each other there was a significantly different proportion of small lesions in the juvenile-

Table IV. Diagnosis by ECG and VCG in diabetics

	Juvenile onset		*Maturity onset*	
	ECG	*VCG*	*ECG*	*VCG*
Normal	27 (84%)	18 (56%)	17 (27%)	1 (1.5%)
Borderline normal	3 (10%)	—	2 (3%)	—
Infarct	—	1 (38%)	11 (17%)	55 (86%)
Possible infarct	2 (6%)	2 (6%)	10 (16%)	5 (8%)
I.V.C.D. type undetermined	—	—	1 (1.5%)	—
L.B.B. block without infarct	—	—	4 (6%)	1 (1.5%)
R.B.B. block without infarct	—	—	4 (6%)	—
Nonspecific ST-T changes	—	—	7 (11%)	—
Digitalis effect	—	—	5 (8%)	—
Pulmonary disease	—	—	1 (1.5%)	—
L.V.H. without infarct	—	—	2 (3%)	(3%)
Totals	32 (100%)	32 (100%)	64 (100%)	64 (100%)

onset as compared to the maturity-onset group ($p < 0.05$). This is due to a predominance of small lesions within the juvenile-onset group and a predominance of large lesions in the maturity-onset group. It should be noted that the abnormalities described occurred in the mid and terminal portions of the loop with about the same frequency as they did in the initial part of the loop.

ECG interpretation. The electrocardiographic interpretations of the cardiologists chosen for this study revealed that in the juvenile-onset group there were no tracings diagnostic of myocardial infarction although there were two tracings interpreted as possibly due to infarction. The tracings of the maturity-onset groups were diagnostic of infarction in 11 cases, while an additional 10 cases were suggestive of infarction. Therefore, the interpretations of the ECG's revealed the suggestion of infarction in only 6 per cent of the juvenile-onset group and 33 per cent of the maturity-onset group. The electrocardiographic interpretations are summarized in Table IV.

Table V. VCG evidence of infarction in a random population

Age	Myocardial infarction			
	Definite	Possible	None	Total
15 to 40	4	1	47	52
41+	7	0	39	46
Total	11	1	86	98

Comparison of ECG with VCG. A comparison of the electrocardiographic (concensus) readings with the vector readings is shown in Fig. 3 and Table IV. There were 67 patients whose VCG's revealed definite evidence of myocardial infarction in the total series. 11 of these patient's ECG's were read as definite infarction and 56 failed to show definite evidence of infarction (Table VII). The diagnoses of possible infarct by either ECG or VCG was

Table VI. Severity of destructive disease as seen on the VCG compared to the duration of diabetes

Duration ( )	Myocardial infarction		VCG diagnosis definite evidence of infarction					Total
	None	Possible						
	0*	P	1	2	3	4	5	
Juvenile onset								
0–10		2	2	1	0	0	0	12
11–20	5	0	2	1	0	0	0	8
21+	6	0	3	3	0	0	0	12
Subtotal	—	—	7	5	0	0	0	—
Totals	18	2			12			32
Maturity onset								
0–10	2	1	2	2	9	11	6	33
11–20	2	3	0	2	5	6	5	23
21+	0	1	0	1	1	0	5	8
Subtotal	—	—	2	5	15	17	16	—
Totals	4	5			55			64

*Criteria for sizes: (0) no infarct, (P) diffuse fibrosis, (1) single small, (2) multiple small, (3) medium ± single small, (4) large or medium and multiple small or multiple medium, (5) large and one or more medium or large [illegible]

called negative for the purpose of the following analysis.

Analysis of ECG misses

AREA Using the activation sequence of Scher and Young[7] and the theoretical model of the VCG proposed by us,[8] it was possible to divide the septum and left ventricle into seven large areas (Fig ?) There was no relationship between the area of infarction as interpreted by the VC(and the accuracy of the ECG (Table VIII) This agrees with the findings of Rubin and Weiss.

SIZE Out of 67 patients from the total series whose VCGs were diagnostic of infarction 34 had small or medium infarcts and 32 (94 per cent) were missed by the ECG (Table VII) There were 33 cases in which the VCG demonstrated single or multiple large lesions and 24 (72 per cent) of these failed to show definite evidence of infarction by the ECG The ECG was more accurate with large lesions than with medium-sized and small lesions and this difference was significant (p < 0 05) This indicates that our current EC(criteria are in general less sensitive to the smaller lesions.

CONDUCTION DEFECTS In four of the 24 cases, the VC(depicted large infarcts and a conduction defect (Table VII) and the ECG showed only the conduction defect without evidence of infarction As previously pointed out by Zinn and Cosby and Rubin and Weiss, conduction defects may mask the EC(diagnosis of infarcts in diabetic patients. However in this study when the ECC diagnosis of infarction in the presence or absence of a conduction defect was compared to the over all ac

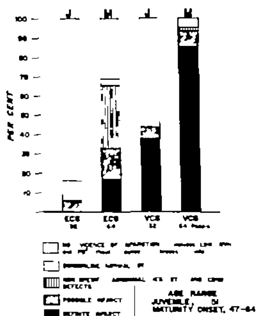


Fig 3

Table VII Infarcts definitely diagnosed by proposed VCG criteria and tabulation of ECG diagnosis of infarction

ECG diagnosis	VCG diagnosis: Medium and small (size 1 2 3)	Large: Single (size 4)	Large: Multiple (size 5)	Conduction defect and large	Total
Definite infarct	2	1	8	( )†	11
Possible or no infarct	32	7	13	4	56
Subtotals		8	1	4	
Totals	34		33		67

Table VII is compreresed ... the definite infarcts diagnosed by the proposed VCG criteria in Table VI
*See Table VI for size classification.
†One case with VCG showing small, and one case with VCG showing ... addition to conduction defect.

*Table VIII Accuracy of ECG related to area of infarction as seen on the VCG**

ECG diagnosis	No. of patients	Area of infarct by VCG							Total infarcts diagnosed by VCG
		1	2	3	4	5	6	7	
Juvenile-onset diabetes									
No infarct	10	3	0	4	2	1	0	1	11
Possible infarct	2	0	0	1	0	0	0	1	2
Definite infarct	0	0	0	0	0	0	0	0	0
Maturity onset diabetes									
No infarct	34	4	0	11	10	6	4	16	51
Possible infarct	10	0	0	0	4	3	0	8	15
Definite infarct	11	6	0	7	3	1	2	7	26

*Patients in this table had definite infarction by the VCG criteria proposed in this paper. The number of infarcts diagnosed is greater than the number of patients in many categories because multiple lesions were diagnosed frequently by the proposed VCG criteria.

curacy of the ECG no relationship was observed. In this series the ECG was as accurate in diagnosing infarction in the presence of a conduction defect as in its absence. The sample size of conduction defects was small, however, and may have obscured a real difference had it been present.

MULTIPLE LESIONS. A total of 13 of the patients had multiple lesions on the VCG's (Table VII), and in such cases it has been suggested by several authors[14,23,24] that a second lesion may produce changes neutralizing the first lesion and hence obscuring either or both lesions by conventional electrocardiographic criteria. However, in our series the statistical analysis of ECG accuracy in the diagnosis of single and multiple lesions failed to show a significant difference between the diagnostic accuracies in the two classes.

We also have no explanation for the additional seven cases in which the VCG showed a single large infarct and the ECG failed to show infarction (Table VII).

The fact that the vast majority of the precordial leads of the ECG's used in this study were recorded at 0.5 cm. per millivolts rather than 1.0 cm. per millivolts may have contributed to the failure of the ECG in some instances.

Discussion

In evaluating VCG's of diabetic patients it was felt that more specific criteria for the diagnosis of myocardial infarction should be formulated. Other authors have described criteria involving dramatic changes in the vectorcardiographic loop and in the cases that have come to autopsy a rather large area of myocardial involvement was usually noted.[7] Burch described the small changes so often seen in the VCG as arcs and dips and suggested that these were due to small myocardial scars. We found no specific criteria, however, with which to evaluate any given VCG for the presence of such small lesions. It was with this in mind that we examined the tracings of clinically normal individuals to determine the amount of potential variation from a smooth loop that could be expected in the normal VCG. From these data the criteria previously described were developed and by these criteria 3 per cent of the clinically normal individuals had evidence of infarction on their VCG's. Two of these were men over 40 years of age and may well have had unrecognized infarctions. An additional 3 per cent were read as questionable.

We also thought it useful to test these criteria against a random population that could include any abnormality with the exception of diabetes. In this group of 98 there were 11 that showed evidence of myocardial infarction. Therefore, testing these criteria in these two populations demonstrated that they were not so inclusive or exclusive as to include a totally unexpected number in the diagnosis of myocardial infarction. A recent report by

Johnson Achor Burchell and Edwards[4] reviewed 1 267 autopsies at the Mayo Clinic with adequate medical records, and found an incidence of definite infarction of 11 per cent. Half of these were unsuspected clinically

In view of the previously demonstrated inaccuracy of electrocardiographic diagnosis of autopsy proved myocardial infarction in diabetic patients, it is not surprising to find this diagnosis made infrequently in the diabetic population of this study in which many have no history of heart disease The high percentage (94 per cent) of persons with maturity-onset diabetes that showed vectorcardiographic abnormalities consistent with infarction on the other hand is consistent with the pathological observation that extensive coronary artery disease is almost universally present in those with maturity-onset diabetes who come to autopsy[7,13,27]

The frequent lack of classical electrocardiographic evidence of infarction in diabetes may be explained in one of three ways, and likely all mechanisms are operative First recent studies[23-25] have shown that there is extensive microarteriolar disease in this group. Blumenthal Alex, and Goldenberg[23] have shown that these lesions involve the coronary arteries as well as the kidneys, central nervous system, retinae and conjunctivae. In such cases, one might expect multifocal fibrosis of the myocardium without large unifocal infarcts. Multifocal fibrosis has been demonstrated in patients with disease in the small intramuscular coronary arteries in the absence of main coronary disease by Domomae Matsumoto and Ueda.[29] Ischemic multifocal fibrosis has also been observed in about one half of patients with the usual variety of main coronary artery narrowing and/or occlusion when careful pathological studies are done such as those reported by Woods, Laurie and Smith[8] and by Ehrlich and Shinolara.[30] Such multifocal disease may well fail to produce the electrocardiographic changes of the classical localized unifocal infarction.

Second when size, as diagnosed by the proposed vectorcardiographic criteria is compared to the ECG diagnosis (Table VIII) it is clear that small abnormal bite out lesions on the VCG consistently failed to produce ECG changes diagnostic of infarction and these were rarely classified as possible infarction. When small and single medium-sized lesions (sizes 1 2 and 3 of Table VI) were lumped together for the entire series, again the inability of the ECG to diagnose such lesions (6 per cent accuracy) is readily apparent (Table VII) The diagnostic accuracy of the ECG on the other hand increased to nearly 40 per cent when multiple large lesions (indicated by the proposed vectorcardiographic criteria) were present. It has been suggested that when multiple infarcts occur a second third or fourth infarct may produce counterbalancing vectors that obscure earlier clear-cut evidence of infarction and leave behind only nonspecific ST and T changes. Our data, however do not support this hypothesis when single large lesions were compared to multiple large lesions, no difference in the diagnostic accuracy of the ECG was found. In summary it appears that the larger the infarct as seen by the VCG and the more evidence for myocardial destruction that there is the greater the accuracy of the ECG.

Third these data indicate that the notion that the diagnosis of infarction is made only from changes in the initial portions (initial 0 04 vector) of the QRS is untenable. With infarction of the basal portions of the septum and left ventricle one would expect changes limited to the terminal QRS Such changes are generated by our model[12] and have also been reported by Burch and associates, [16] Massey and Walsh and others[31-35] (Fig 4 & 5) Infarction of the outer one half of the apex or free left ventricular wall near the apex will produce changes limited to the mid portion of the QRS (Fig 6 & 7) Criteria for infarction such as those proposed in conventional ECG texts which are limited to changes in the initial 0 04 second of the QRS could not be expected to diagnose such infarcts.

The VCG because of it increased gain high frequency oscilloscopic records and it depiction of phase changes between two lead is much more likely to pick up small high frequency "bite outs" or irregularities in the depolarization of the ventricular myocardium such as would occur in single small scars and in multifoc

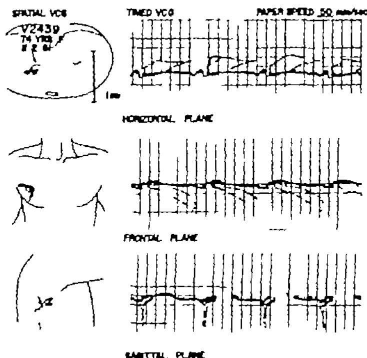


Fig 4 The spatial and timed VCG in this patient reveals notching and slurring in the terminal portion of the QRS that lasts for 10 msec and deviates from smooth loop by 0.1 mv This lesion was classified therefore, as multiple small infarcts mainly in the posterobasal region (area 6) of the left ventricle. This lesion approaches a medium-sized one in over-all loss of posterior basal vectors The initial 0.04 sec of the QRS loop is relatively normal

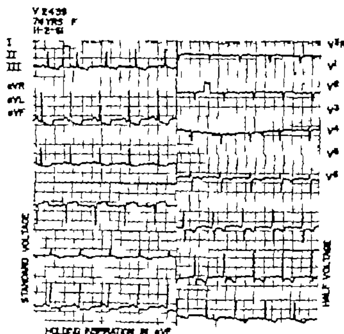


Fig 5 This 13-lead ECG from the same patient whose vector is shown in Fig 4 demonstrates symmetrical T wave inversion in Leads I AVL and V to V The r-wave progression in anterior precordial leads is normal and no diagnostic Q waves are seen. There is slight terminal slurring of the QRS in Leads I II III AVL and V_3R through V_6. Tracing was interpreted as left ventricular ischemia and probable enlargement.

SPATIAL VCG

TIMED VCG

PAPER SPEED 50 mm/sec.

HORIZONTAL PLANE

FRONTAL PLANE

SAGITTAL PLANE

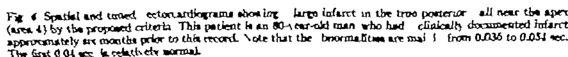


Fig. 6 Spatial and timed ectorcardiograms showing large infarct in the true posterior all near the apex (area 4) by the proposed criteria. This patient is an 80-year-old man who had clinically documented infarct approximately six months prior to this record. Note that the bnormalities are mai from 0.036 to 0.054 sec. The first 0.04 sec. is relatively normal.

V 100
80 YRS. M

I
II
III
aVR
VL
aVF

V3R
V1
V2
V3
V4
V5
V6

STANDARD VOLTAGE

HALF VOLTAGE

HOLDING INSPIRATION III aVF

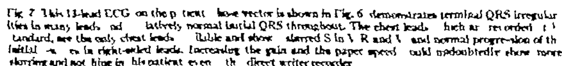


Fig. 7 This 13-lead ECG on the p tient hose vector is shown in Fig. 6 demonstrates terminal QRS irregular ities in many leads nd latively normal initial QRS throughout. The chest leads hich ar recorded t tandard, are the only chest leads ilable and show slurred S in V R and V and normal progression of th initial ve es in right-sided leads. Increasing the gain and the paper speed ould undoubtedly show more slurring and not hing in his patient even th direct writer recorder

Over all the major reason for failure to diagnose infarction by the ECG in this series was attributable to the inability (at any gain) of the conventional direct writer ECG to record high-frequency components. This, coupled with the fact that current accepted ECG criteria for infarction do not include slurs or notches in the QRS or changes in the terminal QRS as diagnostic of infarction accounted for the vast majority of failures of the ECG to diagnose infarctions in this group. In a small percentage the diagnosis of infarction may have been missed because the precordial leads were taken at ½ standard (0.5 cm = 1 mv.) However a review of these ECG's suggests that this was a possible factor in less than 5 per cent of records over all.

It would appear from the work of Langer and co-workers[36] which has been confirmed by Durrer[37] by Corday[38] and by us that the amount of high frequency energy in the ECG is much greater in patients with coronary artery disease. The present study is highly consistent with this hypothesis, and suggests that current ECG recording techniques and instrumentation are badly in need of overhaul. As a first step using options available on most direct writer ECG machines, we propose that all tracings be recorded at 2 cm per millivolt and at a 50 mm per second paper speed to make maximum use of the limited frequency response that is present in such instruments. It is also clear from this study that both ECG and VCG criteria need to be refined to include these small changes, and changes in mid and terminal QRS as well.

It must be emphasized again that these patients do not all have proved infarction by conventional clinical criteria. Myocardial fibrosis and or infarction is assumed on the basis of the known almost universal association of advanced coronary artery disease and maturity-onset diabetes. What is now needed is a careful correlation of these vectorcardiographic changes with complete pathological maps of the myocardium at autopsy such as those done by Ehrlich and Shinohara,[39] and Woods, Laurie, and Smith.[8] It is hoped that this report will stimulate such investigation in a number of centers. The entire field of cardiac electrophysiology would clearly benefit by such a study.

Summary and conclusions

1. New quantitative VCG criteria are proposed for the diagnosis of small and medium-sized myocardial infarcts to supplement criteria for large infarcts previously established by other workers. These changes occurred in the initial and terminal portions of the QRS with about the same frequency.

2. These criteria were tested on a random population and defined the expected number of infarctions.

3. Of the cases of maturity-onset diabetes in the present series, 86 per cent were read as definite infarction by these proposed criteria and 8 per cent were read as possible infarct. Therefore, 94 per cent were at least suggestive of infarction.

4. Of the cases of juvenile-onset diabetes, 38 per cent were read as definite infarction by these criteria and 6 per cent were read as possible. Only small lesions were observed in juvenile-onset cases.

5. Single and multiple large lesions were common in maturity-onset diabetes.

6. The severity of the VCG changes was unrelated to the severity or duration of diabetes in this series.

7. The ECG's were interpreted as possible infarction in only 6 per cent of the cases of juvenile-onset diabetes and as definite or possible infarction in 33 per cent of the cases of maturity-onset diabetes.

8. The ECG's missed 94 per cent of small or medium-sized lesions diagnosed by the VCG in this series, but missed only 62 per cent of those with multiple large lesions.

9. The fourfold increase in accuracy of the VCG in this series is presumed to be due to the greater gain frequency response and two-dimensional vectorcardiographic display and to the use of the proposed criteria which include changes in the entire QRS as diagnostic.

10. It is apparent from these data that current ECG recording instruments are inadequate to record a great deal of potentially useful information at the body surface and attention is called to the urgent need of improving such instrumentation.

11. The ECG's recorded with most direct writers can be significantly improved by

routinely recording tracings at a gain of 2 cm per millivolt and a paper speed of 50 mm. per second.

12. Routine pathological studies are inadequate to find and classify small destructive lesions of myocardium and attention is called to the urgent need of more carefully detailed studies of these lesions to correlate with the type of VCG changes reported in this paper.

Special acknowledgment is given to William Paul Thompson, M.D., Eugene J. Ellis, M.D., and Ezra L. Hoffman, M.D., for their assistance in reading the ECG's in this series.

REFERENCES

1. Marble, A.: Coronary artery disease in the diabetic, Diabetes 4:290, 1955.
2. Aarseth, S.: Cardiovascular renal disease in diabetes mellitus, Acta med. scandinav. (Suppl.) 281, 1953.
3. Rabin, H. B., and Weiss, M. J.: Diabetic patients with myocardial infarction, California Med. 86:254, 1957.
4. Johnson, W. J., Achor, R. W. P., Burchell, H. B., and Edward, J. E.: Unrecognized myocardial infarction, Arch. Int. Med. 103:253, 1959.
5. Agar, J. M.: Silent myocardial infarction in diabetes mellitus, M. J. Australia 49:284, 1962.
6. Bradley, R. F., and Schonfeld, A.: Diminished pain in diabetic patients with acute myocardial infarction, Geriatrics 17:322, 1962.
7. Pathak, S., and Sachar, R. S.: Cardiovascular complications of diabetes mellitus, Brit. M. J. 1228:1505, 1961.
8. Woods, J. D., Laurie, W., and Smith, W. G.: The reliability of the electrocardiogram in myocardial infarction, Lancet 2:265, 1963.
9. Master, A. M., Dack, S., and Jaffe, H. L.: Age, sex, and hypertension in myocardial infarction due to coronary occlusion, Arch. Int. Med. 61:767, 1939.
10. Sievers, J., Blomquist, G., and Biork, G.: Studies on myocardial infarction in Malmo 1935 to 1954, Acta med. scandina. 169:95, 1961.
11. Root, H. F., Bland, E. F., Gordon, W. H., and White, P. D.: Coronary atherosclerosis in diabetes mellitus, J. A. M. A. 113:27, 1939.
12. Weinstein, A.: Coronary artery disease in the diabetic, J. Tennessee M. A. 19:346, 1956.
13. Mortensen, J.: Cardiovascular and renal findings in long-standing diabetes mellitus, Acta med. scandinav. 128:94, 1950.
14. Liebow, I. M., Hellerstein, H. K., and Miller, M.: Arteriosclerotic heart disease in diabetes mellitus, Am. J. Med. 18:438, 1955.
15. Massey, E., and Walsh, T. J.: Clinical vectorcardiography and electrocardiography, Chicago, 1960, Year Book Publishers, Inc., pp. 267 and 317.
16. Lamb, L. E.: Electrocardiography and vectorcardiography, Philadelphia, 1965, W. B. Saunders Company.
17. Hugenholtz, P. G., Whipple, G. H., and Levine, H. D.: A clinical appraisal of the vectorcardiogram in myocardial infarction, I and II, Circulation 24:806, 1961.
18. Burch, G. E., Horan, L., Ablidakov, J. A., and Cronvich, J. A.: A study of the spatial vectorcardiogram in subjects with posterior myocardial infarction, Circulation 12:418, 1955.
19. Burch, G. E., Horan, L., and Cronvich, J. A.: A study of the spatial vectorcardiogram in subjects with anterior myocardial infarction, Circulation 13:360, 1956.
20. Burch, G. E., Horan, L., Ziskind, J., and Cronvich, J. A.: A correlative study of postmortem, electrocardiographic, and spatial vectorcardiographic data in myocardial infarction, Circulation 18:325, 1958.
21. Selvester, R. H., Kalaba, R., Collier, C. R., Bellman, R., and Kagiwada, H.: A mathematical model of the electrical field of the heart with distance and boundary effects, in Vectorcardiography 1965, The Netherlands, 1966, North Holland Publishing Co., p. 403.
22. Scher, A. M., and Young, A. C.: The pathway of ventricular depolarization in the dog, Circulation Res. 4:461, 1959.
23. Durrer, D., van Dam, R. T., van Meijler, F. L., Arzbaecher, R. C., Mueller, E. J., and Freud, G. E.: Electrical activation and membrane action potentials of a perfused normal human heart, read before the American Heart Association, New York, October, 1966, Circulation 34:92, 1966 (abstr.).
24. Zinn, W. J., and Cosby, R. S.: A re-evaluation of the diagnostic accuracy of the electrocardiogram, Am. J. Med. 8:177, 1950.
25. Grant, R. P.: Clinical electrocardiography: the spatial vector approach, New York, 1957, McGraw-Hill Book Company, Inc., p. 155.
26. Lipman, B. S., and Massie, E.: Clinical scalar electrocardiography, Chicago, 1965, Year Book Medical Publishers, p. 251.
27. Liebow, I. M., and Hellerstein, H. K.: Cardiac complications of diabetes mellitus, Am. J. Med. 7:660, 1949.
28. Wells, R., Herman, M. V., and Gorlin, R.: Microvascular changes in coronary artery disease, presented at the American Heart Association, New York, October, 1966, Circulation 34:237, 1966 (abstr.).
29. Rees, S. B., Camerini Davalos, R. A., Caulfield, J. B., Lozano-Castaneda, O., Cervantes-Amezcua, A., Taton, J., Pometta, D., Krauthammer, J. P., and Marble, A.: Pathophysiology of microangiopathy in diabetes mellitus, Ciba Foundation Symposium: Endocrinology (London) 15:315, Boston, 1964, Little, Brown and Company.
30. Berkman, J., and Rifkin, H.: Newer aspects of diabetic microangiopathy, Ann. Rev. Med. 17:83, 1966.
31. Blumenthal, H. T., Alex, M., and Goldenberg, S.: A study of lesions of the intramural coronary artery branches in diabetes mellitus, Arch. Path. 70:27, 1960.

32. Domonae I M tsumoto, Y and Ueda, E. Significance of coronary rteriosclerosis m the tramuscular coronary arteries, Geriatrics 20 179 1965
33. Ehrlich J C and Sh nohara, Y Low incidence of coronary thrombosis m ocardial infarction A restud of serial block tech ique. Arch Path 78:432 1964
34. G af W S and (ther I A pentagon of forces usef l i understand ng the vectorcardiographic effect of myocardial i f rction, Vec torcardiogr phy 1965, Symposium held t the Long Isl nd Jewish Hospital, New York, M 11 13 1965 Amsterdam 1966, North-Holland Publish ng C pp 197 200
35. Young E Williams, C., nd Kossuth-Hopff Diagnostic mild to lat QRS vectorcardiographic abnormalities in old inferior myocardial infarction electrocardiography correlation Circulation 34:243 1966.
36. Langer P H Geselow tz, D B., and M nure F T High frequency components in the elec trocardiograms of normal subject and of patients with coronary heart disease, Am Heart J 62:746, 1961
37. Durrer D The human heart some aspect of ts excitation, T & Studies Coll. Physicians Philadelphia 33 139 1966.
38. Corday E Personal commu ication.

Evolution of clinical radiological, and electrocardiographic changes following experimental atrial septal defect

Allan M Lansing M D Ph.D F.R C S (C)
Louisville Ky

The cause of the incomplete right bundle branch block commonly seen in atrial septal defect has been somewhat controversial The present consensus is that hypertrophy of the outflow tract region of the right ventricle accounts for this phenomenon rather than a congenital defect that interferes with conduction of the impulse through the right bundle branch To elucidate the question of whether the lesion was congenital or acquired atrial septal defects were created in puppies weighing three to five pounds, after which the electrocardiogram (ECG) chest x ray clinical findings and intracardiac pressures were recorded for a $2\frac{1}{2}$ year period (January 1964 to July 1966). Changes that occurred in the ECG were correlated with the evolution of the clinical and radiological findings.

Methods

Ten mongrel puppies from the same litter were the subjects of the investigation In eight of the animals an atrial septal defect was created by the Blalock Hanlon technique while two animals served as nonoperated controls. At the time of operation the animals weighed between three and five pounds and all survived the operative procedure. At intervals of four to eight weeks, sodium thiopental anesthesia was administered the animal was positioned on its back, and the ECG chest x ray and clinical findings were recorded. Right heart catheterization was carried out 6 18 and 30 months after the operative procedure Phonocardiograms were obtained on occasion to confirm the clinical auscultatory findings. The animals received no special medical therapy and were allowed to run freely on a farm where they were fed a standard dog chow At the end of the study period the survivors were painlessly put to death and a postmortem examination was performed.

Results

Eight of the animals survived for the 30 month period of study while two experimental animals died a few hours after an anesthetic had been administered to record the experimental data 27 months after operation. At this time it was obvious that each of these two dogs was in gross congestive heart failure with a markedly enlarged heart tachycardia, a rapid respiratory rate and jugular venous distention

From the Department of Surgery University of Louisville School of Medicine and Price Institute of Surgical Research, [illegible] South Floyd Street, Louisville K[illegible] 40202
Received for publication Aug 3 1967
*Chief of Cardiovascular Surgery

Clinical findings. After induction of sodium thiopental anesthesia each animal was carefully examined and a record made of the neck venous pulsation, liver enlargement, thrills, heart sounds, murmurs, and evidence of dilatation of the right atrium and right ventricle.

DOG 1. Ten months after operation a midsystolic murmur was audible, the second heart sound was more widely split than normal with a pulmonary component that was louder than normal. Evidence of diastolic overfilling of the right ventricle was both visible and palpable at 15 months and a venous "A" wave was visible in the neck at 18 months. At 27 months, a thrill could be palpated at the second left intercostal space and the pulsation of the dilated right atrium was visible to the right of the sternum.

DOG 2. Increased splitting of the second heart sound and increased intensity of the pulmonary component were heard 10 months after operation. At 11 months, a systolic murmur was heard; at 15 months, an "A" wave was visible in the neck. The first heart sound was increased in intensity 27 months after operation, and there was a Grade 2/6 systolic murmur at the second left intercostal space, but the second heart sound varied with respiration, a finding that had not been present three months earlier. This suggested that the heart was still enlarged from the previous volume load, as indicated by the loud first heart sound, but that the shunt was decreasing or absent. In fact, the postmortem examination at 30 months showed that the defect was closed, although cardiac catheterization at 18 months proved that it was open at that time.

DOG 3. A Grade 2/6 systolic murmur appeared 10 months after operation, at which time the second heart sound was more widely split than normal but the pulmonary component was not accentuated. At 15 months, there was wide splitting of the second heart sound and a jugular venous "A" wave was present. At 18 months, dilatation of the right atrium was diagnosed clinically from the presence of an atrial "scratch" or pericardial friction rub best heard to the right of the sternum. Evidence of diastolic overfilling of the right ventricle by palpation and inspection was present 27 months after creation of the defect. The dog was in congestive failure at this time and died while recovering from anesthesia.

DOG 4. Ten months after operation a systolic murmur was first noted, but the second heart sound was still normal. There was no further change in the second heart sound or the murmur until 27 months after operation, when there was evidence of a volume load on the right ventricle and the right atrium by palpation of the precordium and observation of the parasternal areas. The heart sounds were normal at this time, however, although the chest x-ray showed prominence of the main pulmonary artery and the peripheral pulmonary vessels, and there was moderate cardiomegaly, especially involving the right atrium. The atrial septal defect, which was proved to be patent by catheterization at 18 months, was not open at cardiac catheterization or postmortem examination at 30 months.

DOG 5. A systolic murmur appeared at the apex 11 months after operation, and wide fixed splitting of the second heart sound was detected 15 months after operation. At the same time, diastolic overfilling of the right ventricle was present. The right atrium became increasingly prominent by 27 months, at which time the animal was in severe congestive failure and died a few hours after administration of an anesthetic for clinical observation.

DOG 6. A wide split and fixed second heart sound appeared 11 months after operation along with a Grade 1/6 systolic murmur at the upper left sternal border. The findings did not change until 18 months, when a dilated right ventricle characteristic of diastolic overloading was observed. By 27 months, the first heart sound was increased in intensity and the murmur had increased to Grade 2/6.

DOG 7. A Grade 1/6 systolic murmur and increased splitting of the second heart sound were detected 10 months after operation. At 15 months, the first heart sound was increased in intensity and a venous "A" wave was present. At 18 months, the right ventricle showed evidence of diastolic overfilling and classical findings of a large atrial septal defect were present. By 27 months, the pulsations of

the right atrium became visible to the right of the sternum. However although the second heart sound was still more widely split than normal at this time the splitting varied with respiration. This proved to be important because, at post mortem examination three months later the heart was quite large but the defect was small (3 by 5 mm.) which suggested that gradual closure of the defect had been revealed by the changes in the second heart sound

DOG 8 A systolic murmur with increased splitting of the second heart sound and prominence of the pulmonary component appeared at 10 months. A loud first heart sound and a Grade 2 6 systolic murmur were present one month later the findings remained unchanged until 27 months, when the right atrium became visible to the right of the sternum

In summary the first clinical evidence of an atrial septal defect appeared around 11 months after operation. This consisted of a Grade 1 to 2, 6 systolic murmur at the upper left sternal border and increased splitting of the second heart sound with a prominent pulmonary component. In larger defects, diastolic overfilling of the right ventricle became visible to the left of the sternum at 15 to 18 months, and about the same time an A wave appeared in the neck of some of the animals. About 27 months after operation, the dilated right atrium became visible to the right of the sternum in five animals, and two of the dogs that were in gross congestive heart failure (Nos. 3 and 5) died while recovering from the sodium thiopental anesthesia.

Electrocardiographic changes The ECG's of the eight experimental animals were compared to those of the two control litter mates, and also to the reported observations in normal dogs. No significant changes occurred in the two control litter mates The first change to be noted in each experimental animal was either slurring of the QRS complex or T wave inversion or both These appeared sequentially or simultaneously between five and ten months after the operation. Dog 3 developed an inverted T wave in Lead III with slurring of the QRS seven months after operation but the duration of the QRS never exceeded 0 04 second even though this animal died at 27 months of congestive failure with a 10 by 14 mm. atrial defect Incomplete right bundle branch block with widening and slurring

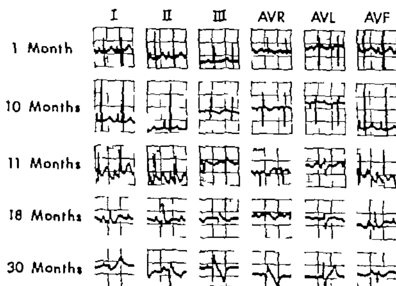


Fig 1 The ECG I Dog 4 at 1 10, 11 18, and 30 months after creation of the atrial defect. Note the sudden widening of the QRS complex between 10 and 11 months and its persistence to 30 months although the defect closed spontaneously about 3 months before.

of the QRS as well as T wave inversion in Lead III developed in seven of the experimental animals. The duration of the QRS increased from 0 04 to 0 08 or 0 10 second quite suddenly in these animals 11 months after operation although it was not present one month earlier. The duration of the QRS never exceeded 0 10 second so complete right bundle branch block was not observed in the 2½ years of this experiment. Once it appeared widening of the QRS was maintained for the duration of the experiment except in one dog. In this animal (No 6) the T wave became inverted at 5 months and the QRS widened to 0 08 second at 11 months but the duration of the QRS decreased to 0 06 second at 18 months, and to 0 04 second at 30 months at which time the T wave became upright. However the clinical findings remained typical of ASD and a large defect was present at autopsy.

A peaked P wave in Lead II that was more than 5 mm in height indicating right atrial hypertrophy occurred in only five of the eight dogs. In four of these this appeared between 10 and 15 months and remained present until termination of the experiment. In one the P wave abnormality was present from 10 to 15 months after operation but was gone by 18 months.

Nodal rhythm or 2 1 heart block occurred in two dogs. In Dog 1 the block was first present seven months after operation and persisted throughout the rest of the experiment. In Dog 2 a varying 2 1 block or nodal rhythm first appeared three months after operation but the rhythm reverted to a normal sinus rhythm six months after the operative procedure.

The typical electrocardiographic evolution is illustrated by the records of Dog 4 in which the defect closed spontaneously around two years postoperatively (Fig 1). The incomplete right bundle branch block

Table I. Findings at cardiac catheterization

Dog No.	Time after operation (mo.)	RA*	RV	PA	Qp/Qs
1	6	5	24/4	24/11	1 3/1
	18	9	30/4	22/9	2 2/1
	30	9	52/8	19/7	3 2/1
2	6	4	20/3	20/6	1 3/1
	18	2	28/3	24/12	1 8/1
	30	9	68/6	22/14	1/1
3	6	4	18/2	18/6	1 4/1
	18	4	28/2	24/10	2 3/1
	30†	—	—	—	—
4	6	3	20 3	20/7	1 2/1
	18	3	26/4	26/10	1 7/1
	30	3	35/5	31/17	1/1
5	6	4	16/2	16/6	1 2/1
	18	7	36/6	28/12	2 4/1
	30†	—	—	—	—
6	6	4	22/3	22/7	1 3/1
	18	4	24/4	22/12	1 5/1
	30	2	21/2	22/10	2 3/1
7	6	3	20/4	20/7	1 1/1
	18	4	30/4	24/14	1 6/1
	30	10	45/8	36/20	1 4/1
8	6	4	20/3	18/8	1 2/1
	18	3	23/2	23/11	1 5/1
	30	8	38/7	33/15	1 8/1

*RA, right atrial mean pressure (mm. Hg); RV, right ventricular pressure; PA, mean pulmonary artery pressure; QP/QS, ratio of pulmonary to systemic blood flow.

†Died at 27 months.

pattern appeared suddenly 11 months after operation and persisted to the end of the study even though changes in the second heart sound suggested that the defect had closed at least three months before completion of the experiment. A similar pattern was observed in the dogs whose defects remained open but not in the control animals.

Cardiac catheterization. The findings at cardiac catheterization performed at 6, 18, and 30 months after creation of the atrial defect are listed in Table I. Mean right atrial pressure was high at 30 months in Dogs 1, 2, and 7. Dogs 1 and 2 had a significant gradient across the right ventricular outflow tract region and an increased ventricular pressure which in Dog 1 was associated with a large shunt. However, in Dog 2 the atrial defect closed at about two years but a 46 mm. gradient remained in the outflow region as evidence of the prior large shunt and right ventricular hypertrophy. This was a unique example of an acquired infundibular stenosis remaining after spontaneous closure of a septal defect. Dog 7 had a small shunt throughout the period of study and the increased right-sided pressures recorded at 30 months were probably related to conditions at the time of the catheterization since microscopic pulmonary vascular changes were not present.

Chest x-ray. The first obvious change in the chest x-ray was increasing prominence of the main pulmonary artery which did not appear until about 10 months after the operative procedure. Over the next five months, that is, up to 15 months after creation of the atrial defect, the right atrium enlarged and the pulmonary vascular markings became more prominent. Gross radiological cardiomegaly was evident in three of the four dogs that had defects 10 mm. in diameter or greater. The cardiomegaly and dilated pulmonary arteries persisted in Dogs 2 and 4, although the defect closed sometime around two years after its creation. Dog 7 was interesting in that the only radiological abnormality was prominence of the right atrium that was first noted 15 months

Table II. Findings at postmortem examination

Dog No.	Phonocardiogram and clinical state at 30 months*						Postmortem findings					
	S1	S2	S3 or S4	Systolic murmur	Diastolic murmur	Comments	Weight (lb.)	Sex	Heart weight (Gm.)	ASD size (mm.)	R. V. thickness (mm.)	L. V. thickness (mm.)
1	++	Wide split, fixed	None	Present	RLSB	Excellent clinical findings	30	F	179	14 11	7	9
	+++	Wide split, varied	None	Present	None	Closed	35	F	210	Closed	7	14
3	+++	Wide split, varied	None	None	RLSB	Died, CHF 27 mo.	30	M	306	10 14	8	11
4	Normal	Normal, varied	None	None	RLSB	Closed	40	M	190	Closed		13
5	Normal	Normal, fixed	S4, apex	None	RLSB	Died, CHF 27 mo.	35	M	226	11 10		15
6	+ split	Wide split, fixed	None	Present	RLSB	Excellent clinical findings	33	F	143	10 L.	6	11
7	Normal	Wide split, varied	None	Present	RLSB apex	Minimal clinical findings	35	F	135	3 8	8	12
	+	Wide split, varied	None	Present	None	Normal findings	40	F	1 5	5 x 3	6	14

*Phonocardiograms and postmortem findings at 27 months in Dogs 3 and 5, which died at this time.

after operation the small defect found at postmortem examination correlated well with both the radiological and clinical findings that had been recorded

Postmortem findings The findings at the time of postmortem examination in the eight experimental animals are listed in Table II The atrial septal defect was still open in six dogs, each of which had a grossly dilated right atrium right ventricle and main pulmonary artery In Dogs 2 and 4 the defect was closed but the right atrium right ventricle and main pulmonary artery were dilated These findings, along with the results of catheterization at 18 months and the clinical findings between 18 months and 24 months, suggested that the defect had closed sometime after two years. Microscopic examination of the pulmonary arterioles revealed no evidence of hypertrophy of the muscular layer or thickening of the intima in any of the animals.

Discussion

The frequent occurrence of incomplete right bundle branch block (RBBB) in patients with atrial septal defect has been a common clinical observation Burch and DePasquale[1] found that 23 of 90 patients had complete RBBB (QRS more than 0.12 second) 29 had incomplete RBBB (QRS greater than 0.10 but less than 0.12 second) 31 had incomplete RBBB but the QRS was less than 0.10 second and seven had a completely normal ECG They observed that complete RBBB occurred primarily in adults over 30 years of age and concluded that both the degree of right ventricular hypertrophy especially of the crista supraventricularis, and the duration of the QRS complex increased with the age of the patient Although analysis of the P wave was not consistently helpful in evaluation of right atrial hypertrophy they reported that the best index of right atrial hypertrophy was a diphasic P wave in Lead V_1 They could not correlate the QRS axis with either the right ventricular pressure or the size of the shunt.

This experiment was designed to determine whether or not the incomplete RBBB was a congenital defect in the conduction system or a developmental change and to correlate the evolution of clinical and radiological changes with the ECG The plan was to create the defect in puppies weighing three to five pounds and follow the clinical radiological and electrocardiographic changes simultaneously for a prolonged period While the experiment was in progress, Boineau and associates[2] reported a one-year study of the ECG and vectorcardiogram (VCG) in adult dogs in which an atrial septal defect had been created Their purpose was to determine the sequence of ventricular activation, correlate this with the VCG and determine if anatomical interruption of the right bundle branch was present. Although clinical and radiological findings were not reported in their experiment, the differences and similarities between the results of the experiments need to be discussed.

The animals used by Boineau and associates[2] were adult dogs weighing 15 to 30 kilograms, whereas in the present study puppies weighing 1.4 to 2.3 kilograms (three to five pounds) at the start of the experiment were employed Atrial septal defects were created in ten of their dogs, five of which died within one to two weeks, apparently in congestive heart failure. Despite the much smaller size of the puppies none of them died in this period and congestive heart failure did not appear until over two years after operation in spite of the fact that the atrial septal defects were proved to be open. The cause of the difference in time of onset may be that the atrial septal defect was relatively larger initially since their operations were carried out under inflow occlusion. It is more likely however that creation of an atrial septal defect in an adult animal is associated with an immediately larger shunt since the right ventricular wall is relatively thinner and more compliant than the left ventricular wall a difference that is not so marked in the newborn animal Their five survivors were then compared to five unrelated dogs which had had sham operations, whereas our eight surviving puppies were compared with two control litter mates that had not been operated upon

Boineau and associates[2] reported the electrocardiographic changes of incomplete

RBBB in each of their five dogs between 7 and 11 months after the operation. These same changes occurred in each of our eight experimental animals but surprisingly although the QRS complex became slurred its duration was not increased in one dog that died in congestive failure with a large atrial septal defect 7 months after operation. The first change in each dog appeared five to ten months after creation of the atrial defect and consisted of inversion of the T wave in Lead III and slurring of the QRS. It is fascinating that widening of the QRS from 0.04 to 0.08 or 0.10 second occurred quite suddenly in seven of the eight experimental animals, not being present in any of them ten months after operation but being found one month later in each one. At the same time that the QRS widening occurred the clinical picture changed with the appearance of wide splitting of the second heart sound and increased intensity of the pulmonary component. This correlates very well with the observation in human subjects that the shunt associated with a secundum atrial defect is usually small in infancy and does not become clinically detectable until sometime after the first year of life. It is postulated that gradual resolution of the fetal state of the pulmonary arteriolar wall and of the right ventricular muscle allows the development of an increasing shunt in this period a hypothesis that draws support from the observations of this experiment.

The gross pathological findings in both experimental series were comparable. The right ventricle and right atrium were dilated, as was the main pulmonary artery. The thickness of the right ventricle in our puppies was 6 to 8 mm compared to a normal of 3 to 4 mm and the free wall of the left ventricle was 9 to 15 mm. compared to the 10 to 1 mm in the two control litter mates.

Pulmonary hypertension did not develop in our animals even 2½ years after creation of the atrial septal defect although marked dilatation of the main and peripheral pulmonary arteries occurred. Even the two that died of severe congestive heart failure did not have an elevated pulmonary artery pressure. Microscopic examination of the pulmonary arterioles of the experimental animals revealed no evidence of medial hypertrophy or intimal thickening when compared to the two control litter mates. These findings of course correspond to the clinical observation that pulmonary vascular changes (and complete right bundle branch block) occur very late in patients with secundum atrial septal defects, being found primarily in adults over 30 years of age.

The observations in the two dogs in which spontaneous closure occurred 24 to 27 months after operation are important in determining the clinical changes that might be detected following surgical closure of the defect. Despite spontaneous closure of the defect in these dogs, the chest x-ray still showed cardiomegaly and dilated pulmonary vessels several months later and the ECG did not change. Examination of the precordium still showed evidence of a dilated right ventricle and right atrium in the parasternal areas. However significant changes in second heart sound were recorded in spite of the fact that at the time it was not known that the defect had closed. In both dogs the pulmonary component of the second heart sound became softer, splitting of the second heart sound became less and respiratory variation in splitting was noted. In one of these dogs the systolic murmur and thrill continued to be present and the first heart sound was still increased and this was the animal in which infundibular stenosis developed and persisted after the atrial defect closed. Dog 7 after initial evidence of a good shunt showed respiratory variation in the splitting of the second heart sound at 27 months although the pulmonary component remained loud and the second sound was still more widely split than normal. In this dog only a small defect was present at postmortem examination (30 months) and presumably gradual spontaneous closure was occurring, the first evidence for which was respiratory variation in the splitting of the second sound.

Similar observations have been made in patients who have undergone open heart closure of an atrial defect. Postoperative regression of the size of the heart, main pulmonary artery and the

peripheral vessels is slow. A faint systolic murmur may still be present because of turbulence caused by the dilated pulmonary artery. However, the character of the pulmonary component of the second heart sound changes immediately after operation in that its intensity decreases and the snapping quality disappears. At the same time respiratory variation in the splitting of the second sound appears, although the split may still be wider than normal.

The etiology of the RBBB was documented by Boineau and associates[2] in studies of the sequence of ventricular activation performed by direct insertion of needle electrodes into the right ventricular muscle at thoracotomy. The total right ventricular activation time was increased to 43 to 46 msec. (normal 33 to 36) and invasion of the crista and the high outflow tract occurred 2 to 4 msec. later than normal. They found no evidence of a conduction delay; the right bundle branch appeared grossly normal when stained with iodine, and the speed of conduction through the free wall of the right ventricle was normal. They ruled out the importance of the greater distance traveled over the endocardial surface of the dilated chamber as a cause for the RBBB, and it was their conclusion that the greater thickness of the free wall of the outflow tract undergoing activation at a normal rate accounted for the more prolonged total activation time in patients and animals with atrial septal defects.

If right ventricular hypertrophy accounts for incomplete RBBB in atrial septal defect, why is it not present in patients with pulmonary stenosis or primary pulmonary hypertension? In fact, it has been observed in patients with mild to moderate pulmonary stenosis in at least one third of the cases.[6,7] However, it is not present in more severe cases of pulmonary stenosis or primary pulmonary hypertension where the S wave is lost in Lead V_1 as the R wave becomes increasingly high. Consequently, incomplete RBBB may be an indication of mild hypertrophy of the right ventricular outflow tract that is masked in more advanced forms of diffuse right ventricular hypertrophy associated with moderately severe pulmonary stenosis or pulmonary hypertension.

On the other hand, absence of incomplete RBBB in the ECG does not rule out atrial septal defect, a fact that has been observed clinically by Burch and DePasquale[1] and experimentally in these dogs. Dog 3 developed slurring of the QRS and T wave inversion, but the duration of the QRS never exceeded 0.04 second even though this animal had a large defect at postmortem examination. Dog 6, which also had a large atrial defect, had widening of the QRS from 0.04 to 0.08 second at 11 months, narrowing to 0.06 second by 18 months, and return to 0.04 second by 30 months. Thus, increased duration of the QRS complex may be transient or absent even in the experimental situation, although a change in the QRS with slurring of its configuration developed in all of the animals.

Summary

Incomplete RBBB associated with atrial septal defect is a developmental abnormality that results from mild right ventricular hypertrophy, particularly in the outflow tract region. This electrocardiographic finding appeared five to ten months after surgical creation of the atrial defect in eight puppies. At 11 months, widening of the QRS appeared suddenly at the same time that the pulmonary valve closure became louder, sharper, and delayed so that the defect could be detected clinically. Gradual spontaneous narrowing of a surgically created atrial septal defect in the experimental animal was suspected from the appearance of respiratory variation in splitting of the second sound, even though the splitting was still greater than normal. Complete spontaneous closure of the defect in the experimental animal or surgical repair in man is immediately followed by decreased intensity and a softer quality of the pulmonary component of the second heart sound, although the radiological and electrocardiographic evidence of the previous defect persists.

The author wishes to thank Dr. Laman Gray, Jr., who assisted with the project during two summers as a student research scholar. Support for the project came principally from a Markle Foundation Scholarship awarded to the author.

REFERENCES

1. Burch G. E., and DePasquale N. The electrocardiogram and ventricular gradient in atrial septal defect, AM. HEART J 58:190 1959
2. Boineau, J P Spach, M. S and Ayers, C. R. Genesis of the electrocardiogram in atrial septal defect, AM. HEART J 68:637 1964.
3. Blalock, A and Hanlon, C. R. The surgical treatment of complete transposition of the aorta and pulmonary artery Surg Gynec. & Obst. 90 1 1950.
4. Borman, S. O Paragopoulos, P and Kahn, S The electrocardiogram of the normal dog J Thoracic & Cardiovas. Surg 51:379 1966
5. Keith J D Rowe R. D and Vlad, P Heart disease in infancy and childhood, New York, 1958, The Macmillan Company
6. Nadas, A. S. Pediatric cardiology Philadelphia, 1963, W B Saunders Company
7. Gasul, B M Arcilla, R. A and Lev M Heart disease in children. Diagnosis and treatment, Philadelphia and Montreal, 1966 J B Lippincott Company

Digitalis toxicity

II The effect of metabolic alkalosis

Merritt C Warren M.D
Ralph E Gianelly M D
*Sherilyn L. Cutler M.A ****
*Donald C Harrison M D *****
Palo Alto Calif

Digitalis glycosides remain the most widely used therapeutic agents in the treatment of congestive heart failure In recent years the effects of metabolic abnormalities on susceptibility to digitalis intoxication have been emphasized [1,2] Major stress has been placed on serum and total body electrolytes. Studies on the effects of aberrations in pO pCO$_2$ and pH on the amount of digitalis necessary to produce toxicity have been performed These have primarily tested the effects of acidosis induced by breathing gas mixtures containing high concentrations of carbon dioxide. The effect of metabolic alkalosis on the amount of digitalis necessary to produce toxicity has been investigated [3] The duration of toxicity however has not been studied In addition the experimental conditions were not optimal because blood gases were incompletely monitored and the animals were not used as their own controls. Accordingly the influence of metabolic alkalosis on susceptibility to digitalis toxicity and duration of such toxicity in dogs has been studied in this investigation

Methods

Studies were performed in 19 dogs (12.3 to 23 4 kilograms) anesthetized with pentobarbital The initial dose was 30 mg per kilogram and small supplemental doses were given as necessary to maintain a light plane of anesthesia. Arterial pressure was measured with a P23Db Statham pressure transducer connected to a PE No. 260 cannula in the femoral artery Standard Lead II of the ECG and arterial pressure were recorded by means of a multichannel Beckman model R direct writing oscillograph Ventilation was maintained through a cuffed endotracheal tube with a Harvard respirator Samples from the femoral arterial cannula were analyzed for pO$_2$ pCO$_2$ pH K$^+$ and Mg^{++} These were collected

From the Departments of Medicine and Pediatrics, Stanford University School of Medicine, Palo Alto, Calif 94304
Supported in part by Grants HE-09058-03, HE 5709-01 and 5-T1-HD 49-07 from the National Heart Institute and grant from the Hartford Foundation.
Received for publication April 12, 1967
*Assistant Professor Department of Pediatrics, Loma Linda University School of Medicine Loma Linda, Calif. (present address).
**Research Fellow Cardiology Division, Stanford University School of Medicine, Palo Alto, Calif.
***Research Assistant, Cardiology Division, Stanford University School of Medicine Palo Alto, Calif
****Chief Cardiology Division, Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif (Address communications to Dr Harrison)

three times during the control (lactated Ringer's infusion) experiments initially after infusion of a volume of Ringer's solution which was approximately equal to the volume of sodium hydroxide calculated to produce the desired level of alkalosis, and at the onset of digitalis toxicity During the alkalosis (sodium hydroxide infusion) experiments, five or six blood samples were obtained for analysis at the beginning, at intervals during the infusion of sodium hydroxide until the desired degree of alkalosis was obtained and at the time digitalis toxicity developed. The volumes of sodium hydroxide and Ringer's solution infused in these experiments were approximately equal averaging 295 ± 78 and 243 ± 84 ml. in each group respectively These solutions were infused into the jugular veins

The blood *p*H *p*CO and *p*O were determined with a model AME 1 Astrup ultramicro apparatus. The pH and pCO were determined by the method of Astrup and associates. The pH electrode was calibrated daily with standard solutions and duplicate pH determinations on blood samples were found to vary by no more than ± 0.01 pH unit. The pO_2 was determined with a modification of the Clark pO_2 electrode and duplicate determinations varied by no more than ± 2 mm. Hg The serum potassium and magnesium were determined with an atomic absorption spectrophotometer (Perkin-Elmer model 290) In each experiment two infusions were given acetylstrophanthidin and NaOH (alkalosis) or lactated Ringer's (control) After a volume of NaOH sufficient to elevate the pH above 7.50 or an equivalent volume of lactated Ringer's was delivered, acetylstrophanthidin (123 μg per minute) was injected into a femoral vein with a Harvard infusion pump until ventricular tachycardia occurred. Identical infusion rates were used in all studies so that this variable could be eliminated in considering the dose to toxicity and the duration of toxicity The ECG was monitored on a multichannel oscilloscope. Ventricular tachycardia for these experiments was defined as the occurrence of four consecutive ventricular ectopic beats. Recovery from ventricular tachycardia was considered to have occurred when less than six ectopic beats per minute were recorded for three consecutive minutes. There were two kinds of experiments

Studies to determine toxic dose A total of 32 infusions of acetylstrophanthidin were made into eight dogs. Each dog was given four infusions—two on the first day and two seven days later Half of the animals received sodium hydroxide (0.33 molar) until the pH had risen above 7.50 Then the administration of acetylstrophanthidin was begun. Both infusions were stopped at the onset of toxicity At least three hours were allowed to elapse following recovery from the arrhythmia before a second infusion was given The second infusion consisted of lactated Ringer's solution containing the following concentration of ions (in milliequivalents per liter) sodium 130 potassium 4 calcium 3 chloride 109 lactate 25 Acetylstrophanthidin was again administered to toxicity On the day following these infusions all animals were anorexic, but by the second day all were eating normally During the following six days they were fed a normal animal diet. One week later the same procedure was carried out with one exception the lactated Ringer's preceded the sodium hydroxide infusion. The other half of the animals had similar experiments with the order reversed that is, the lactated Ringer's preceded the sodium hydroxide infusion the first week and followed it the second No other experimental condition was changed

It was found that the experimental regime was too rigorous for successful completion of the four part experiment when digitalis toxicity was allowed to go without interruption especially when the animal was alkalotic Consequently most of the eight dogs were treated with lidocaine infusions after five minutes of toxicity Since three hours were allowed to pass before the next study the effects of lidocaine were considered to have disappeared before the second study This regime was followed for two reasons (1) to permit each dog to act as his own control and (2) to eliminate the length of anesthesia with accompanying manipulation as a variable factor No dog which had deteriorated physically in the week between the experiments was used for the second set of experiments.

Table I Acetylstrophanthidin to produce ventricular tachycardia

N	Ringer A.M.	NaOH P.M.	NaOH A.M.	Ringer P.M.
7	54 9	45 5	53 3	64 4
8	45 0	59 0	52 0	46 7
9	69 5	67 5	53 3	58 8
10	51 4	65 4	63 0	68 2
11	58 8	43 8	54 1	24 0
12	84 0	58 6	62 5	68 6
14	55 5	39 6	46 5	31 8
15	70 0	69 0	67 0	56 1
Mean and standard error	61 1 ± 6	56 0 ± 5†	56 5 ± 3	52 3 ± 7†

*Dose in micrograms per kilogram of body weight
†Second dose not significantly different from first dose

Studies to determine the duration of toxicity A total of 16 infusions of acetylstrophanthidin were carried out in 11 dogs and duration of toxicity without treatment was ascertained In five of these dogs the full sequence of experiments was done. The other six dogs, however were used only for part of the sequence

Statistical analysis of the data obtained in this study was performed with an IBM 360 50 digital computer This computer was programmed to calculate mean and standard errors and to perform a paired t test analysis.

Results

Studies to determine toxic dose In eight dogs (each receiving four separate infusions of acetylstrophanthidin) the dose required to produce ventricular tachycardia during alkalosis was not significantly different from the dose required when the pH was normal (Table I) There was a tendency for the dose necessary to produce toxicity to be less in the afternoon than in the morning This tendency was present for both the normal and the alkalotic states. The results were highly variable, however and no significant decrease could be demonstrated ($p > 0\ 05$) (Table I) Other studies from this laboratory have shown that when the pH is normal there is no change in the dose of acetylstrophanthidin necessary to produce toxicity if a period of three hours is allowed between recovery and the second infusion.

The arterial pH in the normal and alkalotic studies averaged 7.38 and 7 57 respectively at the onset of ventricular tachycardia. The average pO was greater than 90 mm Hg during all infusions of acetylstrophanthidin and the pCO_2 was less than 45 mm Hg during all infusions (Table II) The heart rates slowed significantly ($p < 0\ 05$) during the infusion of acetylstrophanthidin prior to the onset of ventricular tachycardia in all except those which received Ringer's solution in the afternoon The rate of the ectopic ventricular tachycardia observed one minute after its onset varied widely (Table II)

The mean arterial blood pressures increased significantly ($p < 0\ 05$) during digitalization in those animals in which the pH was normal (Table II) No significant change in pressure however was observed during digitalization after alkalosis had been induced (Table II)

Serum potassium increased significantly during the infusion of acetylstrophanthidin in normal and alkalotic animals ($p < 0\ 05$) In every study the serum potassium was decreased significantly by the infusion of sodium hydroxide ($p < 0\ 05$) The serum magnesium values were not significantly altered by either alkalosis or acetylstrophanthidin infusion (Table II)

Studies to determine the duration of toxicity The average duration of toxicity was greatly prolonged when the animals were alkalotic (Table III) Five of these animals were their own controls and the duration of toxicity was prolonged during alkalosis in all. One animal developed

Table II. Blood gases, electrolytes, and hemodynamic variables

Parameter	Condition	Ringer A.M.	NaOH P.M.	NaOH A.M.	Ringer P.M.
pH unit	C*	7.35†	7.35	7.34	7.41
	O	7.36	7.57	7.56	7.41
K^+ (mEq./L.)	C	3.8	3.4	4.6	4.2
	Pd	3.7	2.5	3.2	4.0
	O	4.6	3.2	3.6	4.9
Mg^{++} (mEq./L.)	C	2.3	0	2.1	0
	O	2.2	2.0	2.0	2.1
Mean arterial pressure (mm. Hg)	C	142	141	136	129
	O	156	141	138	160
Heart rate (beats/min.)	C	169	175	174	181
	O	124	151	146	176
pCO_2 (mm. Hg)	C	43	42	45	45
	O	38	38	42	42
pO_2 (mm. Hg)	C	106	99	101	90
	O	106	93	105	93

*Abbreviations: C, control; O, at onset of ventricular tachycardia; Pd, after infusion of Ringer's or sodium hydroxide but prior to acetylstrophanthidin infusion.
†All values represent the mean of 8 determinations.

Table III. Duration of ventricular tachycardia

Control		Alkalosis	
pH (units)	Duration (min.)	pH (units)	Duration (min.)
7.43	7	7.59	20
7.39*	33	7.56	43
7.38	21	7.61	62
7.28	14	7.62	90
7.37	26	7.72	42
7.36	16	7.59	34
7.35	38	7.52	74
7.40	16	7.75	18†
Mean 7.36‡	19‡	7.60*	52‡

*Paired animals having infusion during normal and alkalotic conditions.
†Died of ventricular fibrillation.
‡Difference significant (p < 0.05).

ventricular fibrillation while alkalotic and could not be resuscitated. This was the only animal in the series to develop ventricular fibrillation.

Electrocardiographic changes. The electrocardiographic sequence of events which usually occurred during the administration of acetylstrophanthidin began with ST segment depression, gradual sinus slowing, and prolongation of the PR interval. This was followed by occasional ventricular premature beats and then the sudden onset of ectopic ventricular tachycardia with AV dissociation (Fig. 1). Some dogs exhibited a different sequence, such as abrupt onset of ventricular tachycardia without occasional premature ventricular contractions. The sequence exhibited by a given dog, however, was usually constant from experiment to experiment.

Discussion

In these studies the production of alkalosis did not increase the animals' sensitivity to acetylstrophanthidin as measured by the amount required to produce ventricular arrhythmia (Table I). These findings are in contrast to findings of other investigators[4] who reported that the hypokalemia occurring during alkalosis reduced the amount of acetylstrophanthidin necessary to produce ventricular arrhythmias. This discrepancy may be explained by the fact that other investigators[4,5] did not use the same animals for control and alkalotic studies and did not measure or control pO_2. We observed wide variations

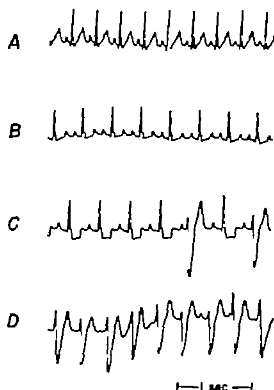


Fig. 1. ECG illustrating typical changes during an infusion of acetylstrophanthidin are shown. A, Control tracing. B, early ST-T changes with slight prolongation of the PR interval and a slowing of the heart rate. C, beginning digitalis toxicity with further slowing, greatly prolonged PR interval and marked ST-T changes (two coupled ventricular premature beats occurred at this time). D, ventricular tachycardia which developed abruptly.

in the amount of acetylstrophanthidin necessary to produce ventricular tachycardia in normal and hypoxic dogs.[8]

The use of each dog as his own control was considered to be necessary to overcome the wide individual variations in the amounts of acetylstrophanthidin required to produce toxicity. It is our conclusion that alkalosis acutely induced by an infusion of sodium hydroxide did not alter the animals' susceptibility to arrhythmias induced by acetylstrophanthidin.

The induction of alkalosis produced a fall in serum potassium in all studies, a finding which is similar to that observed by others.[4,10] Normal serum potassium values in dogs have been reported as 4.6 ± 0.8 mEq. per liter.[9] It is likely that intracellular potassium increased slightly, although this was not measured in these studies. Alkalosis with its accompanying hypokalemia did not alter the expected elevation in the serum potassium occurring during the infusion of acetylstrophanthidin. The magnitude of this increase was similar in both normal and alkalotic conditions and is comparable to the rise noted by other observers.[9,11,12] This increase has been attributed to an increase in the loss of potassium from the cell resulting from blockage of the re-entry of potassium by the acetylstrophanthidin.[12,13]

The failure of the serum magnesium to change significantly during digitalization is in contrast to the decreases reported by Kleiger and associates.[9] No explanation for these differences is apparent.

The rise in arterial pressure produced by the infusion of acetylstrophanthidin in the animals with normal pH's has been observed by other investigators.[13,14] This has been attributed to the peripheral vasoconstrictive action of digitalis glycosides. In our studies no significant increase in arterial pressure was observed during acetylstrophanthidin infusion in alkalotic animals (Table II). It is possible that the alteration in pH prevented the vasoconstrictive action of acetylstrophanthidin.

The duration of ventricular arrhythmias induced by acetylstrophanthidin was prolonged by alkalosis in all five dogs in which studies in both the normal and alkalotic states were made. The average duration of toxicity during alkalosis was almost three times that observed at a normal pH. One animal developed ventricular fibrillation after infusion with acetylstrophanthidin during alkalosis. These studies do not provide for speculation regarding the role of the alkalosis separate from the hypokalemia since these occurred concomitantly and no independent studies were carried out.

Although the mechanism by which the toxic effect of digitalis was prolonged is not defined by this study, the following hypotheses are suggested. Alkalosis clearly causes hypokalemia and the transport of acetylstrophanthidin out of cardiac cells may be impaired by the hypokalemia. It is known that the transport mechanisms for potassium and digitalis are closely interrelated.[15,16] In the presence of metabolic alkalosis there is a shift of hydrogen and

sodium from the cell to the extracellular fluid and a concomitant movement of potassium into the cell. Given a constant total body potassium maintenance of a low concentration of potassium in the extracellular fluid requires that the influx of potassium and the efflux of sodium and hydrogen all remain at high levels. The presence of increased potassium transport during alkalosis may impair the egress of acetylstrophanthidin and therefore prolong toxicity. Another possible explanation is that the altered intracellular electrolyte concentration results in a reduced metabolism of acetylstrophanthidin or an altered binding of the intracellular digitalis glycoside. The present study does not confirm or deny these speculations.

We conclude, then, that metabolic alkalosis prolonged the duration of toxic ectopic ventricular arrhythmias induced by acetylstrophanthidin and that the mechanism for this action is not understood at this time.

There are two clinical conditions to which these data may be applied. First, cardiac arrest frequently occurs in patients who are taking digitalis glycosides or who have toxic arrhythmias due to digitalis. In the resuscitation attempts, these patients are administered large volumes of sodium bicarbonate and occasionally develop alkalosis. Our studies would suggest that the toxicity to digitalis might be enhanced. Secondly, respiratory alkalosis frequently develops in patients with obstructive pulmonary vascular disease due to hyperventilation and alteration in digitalis toxicity may develop.

Summary

The influence of metabolic alkalosis on the amount of acetylstrophanthidin necessary to produce ventricular tachycardia was studied in anesthetized dogs. Although an infusion of sodium hydroxide to produce an average pH of 7.57 resulted in hypokalemia, no significant difference in the amount of acetylstrophanthidin necessary to cause digitalis toxicity during control and metabolic alkalosis was noted. Acute digitalization produced an elevation of serum potassium, a slower heart rate, and an increase in arterial blood pressure.

The duration of ventricular arrhythmias caused by acetylstrophanthidin, however, was greatly prolonged in the alkalotic animals. Possible mechanisms to explain this observation were discussed.

The acetylstrophanthidin used to produce digitalis toxicity in these studies was kindly supplied by Dr. G. C. Chiu, Eli Lilly & Co., Indianapolis 6, Ind.

REFERENCES

1. Lown, B., and Levine, S. A.: Current concepts in digitalis therapy, Boston, 1954, Little, Brown & Company.
2. Rodensky, P. L., and Wasserman, F.: Observations on digitalis intoxication, Arch. Int. Med. 108:171, 1961.
3. Baum, G. L., Dick, M. M., Blum, A., Kaupe, A., and Carballo, J.: Factors involved in digitalis sensitivity in chronic pulmonary insufficiency, Am. Heart J. 57:460, 1959.
4. Bliss, H. A., Fishman, W. E., and Smith, P. M.: Effect of alterations of blood pH on digitalis toxicity, J. Lab. & Clin. Med. 62:53, 1963.
5. Taleo, P. J., Remenchik, A. P., and Cattilletta, A.: Altered myocardial potassium gradients in acute alkalosis and their relationship to acetylstrophanthidin sensitivity in the dog, Circulation 26:794, 1962.
6. Astrup, P., Jorgensen, K., Andersen, O. S., and Engel, K.: The acid-base metabolism. A new approach, Lancet 1:1035, 1960.
7. Jansen, D. J.: Direct pO_2 and pCO_2 measurement, Laboratorium 3:1, 1963.
8. Harrison, D. C., Robinson, M. C., and Kleiger, R. E.: Role of hypoxia in digitalis toxicity, Circulation 34 (suppl. III):134, Oct. 1966.
9. Kleiger, R. E., Seta, K., Vitale, J. J., and Lown, B.: Effects of chronic depletion of potassium and magnesium upon the action of acetylstrophanthidin on the heart, Am. J. Cardiol. 17:520, 1966.
10. Tobin, R. B.: Varying role of extracellular electrolytes in metabolic acidosis and alkalosis, Am. J. Physiol. 195:685, 1958.
11. Lown, B., Whipple, G. H., Lemore, G., and Levine, S. A.: Effects of digitalis upon body electrolytes, Circulation Res. 9:522, 1961.
12. Grupp, G., and Charles, A.: Effect of ouabain and 3-acetylstrophanthidin on potassium exchange in the dog heart in situ, J. Pharmacol. & Exper. Therap. 143:356, 1964.
13. Conn, H. L.: Effect of digitalis and hypoxia on potassium transfer and distribution in the dog heart, Am. J. Physiol. 184:548, 1956.
14. Caruso, A. B., Jr., Love, W. D., and Burch, G. E.: The effects of acetylstrophanthidin on the kinetics of potassium and Rb^{86} in the myocardium of dogs, Am. Heart J. 59:404, 1960.
15. Ross, J., Jr., Waldhausen, J. A., and Braunwald, E.: Studies on digitalis. I. Direct effects on the peripheral vascular resistance, J. Clin. Invest. 39:930, 1960.
16. Dock, W., and Tainter, M. L.: The circulatory changes after full therapeutic doses of digitalis with critical discussion of views on cardiac output, J. Clin. Invest. 8:467, 1930.

The effect of inorganic phosphate infusion upon digitalis-induced arrhythmias in dogs

*Dieter Burckhardt, M.D.**
*John S. LaDue, M.D., Ph.D., F.A.C.C.***
New York, N. Y.

Since Withering's[1] description of the toxic effects of digitalis, many measures for treatment of digitalis-induced arrhythmias have been reported. Parasympatheticolytic drugs antagonize digitalis-increased vagal tone; potassium and magnesium[2] help regulate the automaticity of the heart; and muscle depressants such as quinidine, procaine, procainamide, and lidocaine control abnormal myocardial irritability.

Digitalis tolerance has been increased in man and animals by the administration of reserpine, estrogen, citrate salts, ajmaline,[6] diphenylhydantoin,[7] potassium, and β adrenergic blocking agents.[8-10]

Cohen and co-workers[11] suggested that the antagonistic action of ethylenediaminetetracetic acid (EDTA) on the digitalis effect upon the normal human ventricle was due to reduction of ionized calcium. Goldsmith and Ingbar[12] demonstrated that infusion of inorganic phosphate for the hypercalcemia of metastatic bone involvement, of hyperparathyroidism, and of vitamin D intoxication resulted in a marked decrease in serum calcium.

The purpose of this study was to investigate the effect of inorganic phosphate infusions in dogs upon the toxicity of progressive increments of intravenous digoxin.

Material and methods

Control group. A total of 17 female dogs weighing 8.1 to 22.5 kilograms were anesthetized with 260 to 650 mg. of sodium pentobarbital intravenously and intubated. An infusion of 0.1 ml. per kilogram per minute of 5 per cent dextrose was started, then 0.1 mg. of digoxin was injected into the infusion tubing and readministered every five minutes until an arrhythmia appeared on the continuous electrocardiogram (ECG). The infusion was discontinued when normal sinus rhythm reappeared or after six hours if the dogs had persistent arrhythmias. The onset and duration of the arrhythmia was recorded. Serum potassium, calcium, CO_2, and pH levels were determined prior to starting the infusion and after the cessation of arrhythmia or at the end of six hours. Serum magnesium was also measured in four animals.

Treated group. Two weeks later, the same

From the Department of Medicine, Memorial Hospital, Division of Clinical Investigation, Sloan-Kettering Institute, New York, N. Y.
This investigation was supported by United States Public Health Service research grant No. HE-01978-11 from the National Heart Institute.
Received for publication May 11, 1967.
*Resident in Cardiology, Memorial Hospital for Cancer and Allied Diseases; Visiting Research Fellow, Sloan-Kettering Institute for Cancer Research.
**Associate Professor of Clinical Medicine, Cornell University; Associate Attending Physician, Memorial Hospital for Cancer and Allied Diseases; Associate, Sloan-Kettering Institute for Cancer Research.

animals were studied in exactly the same fashion except that an infusion of 0.1 ml per kilogram per minute of disodium and monopotassium phosphate (0.081M of Na_2HPO_4 plus 0.019M of KH_2PO_4 per liter in water at pH 7.4) instead of 5 per cent dextrose in water was given until disappearance of arrhythmia. If the arrhythmia persisted infusion was stopped after six hours.

Seven dogs in this group failed to develop arrhythmia after receiving the predetermined maximum dose of 0.1 mg digoxin per kilogram intravenously. One animal inadvertantly was given 0.15 mg per kilogram without producing arrhythmia.

Recontrol group. Two weeks were allowed for the clearance of digoxin and the same dogs underwent the study described for the control group, each dog being his own recontrol. In three dogs, normal saline was substituted for 5 per cent dextrose in the recontrol period. Phosphate levels were measured in the same animals in control, treated, and recontrol experiments in addition to the other modalities mentioned above.

Results

Digoxin mortality. Four dogs died during or after the initial control experiment and three dogs died during the recontrol tests. Therefore seven animals died during one of the 30 untreated experiments, a mortality rate of 23.3 per cent. None of the treated animals died as a result of digoxin administration during the 13 experiments when phosphate infusion was given.

The data obtained from the animals that died during the initial control study were excluded.

Digitalis tolerance. Digitalis tolerance in this study is expressed as the time of onset and duration of arrhythmia in minutes compared to the amount of digoxin in milligram required to induce arrhythmia.

Seven of 13 dogs failed to develop arrhythmia during the treated test after the predetermined amount of 0.1 mg of digoxin per kilogram of body weight was given. Nevertheless, the total amount of digoxin* given to these treated animals was an average of 0.34 mg or 25 per cent greater than in the control or recontrol tests. The total dosages varied from 1.4 to 2.0 mg in the treated and from 0.6 to 1.9 mg. in the control and recontrol experiments.

The six dogs which developed arrhythmias despite phosphate treatment required an average of 0.41 mg of the total dose or 30 per cent more digoxin than during the control experiments. The increase in digoxin tolerance during phosphate treatment was highly significant whether compared with control or recontrol tests ($P < 0.001$ and $P < 0.01$ respectively). The observed difference was even greater than the tests of significance imply be-

*Greater amounts of digoxin were not administered because of the danger of fatal outcome.

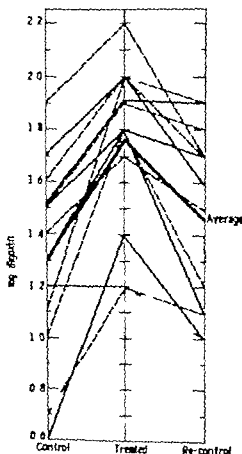


Fig. 1. The dashed lines represent animals which failed to develop this irregularity during phosphate infusion after receiving 0.1 mg. of digoxin per kilogram body weight. The solid lines represent dogs which developed arrhythmias during the control, treated, and recontrol experiments. All dogs showed arrhythmias during the two control studies.

cause seven of the 13 dogs under phosphate treatment tolerated the maximum predetermined dose of digoxin without developing arrhythmia. Fig 1 compares the digoxin dosage given during the control treated and recontrol experiments. All 13 animals developed arrhythmias during the control and recontrol studies but only six when phosphate infusion was given.

The *onset of arrhythmia* in the six dogs showing a rhythm irregularity during the treated test was an average of 21 minutes or 30 per cent delayed. This has the same significance as the digoxin dosage analyses (P < 0 01)

The *duration of arrhythmia* was also studied as a criterion of the effect of phosphate treatment and was an average of 60 minutes (27 per cent) shorter (Fig 2) The observation that seven of 13 dogs failed to show arrhythmia during phosphate treatment when given up to the maximum predetermined digoxin dose can be contrasted to the observation that all 13 dogs in control and recontrol tests developed arrhythmias. This contrast alone established that the observed effect of treatment was statistically significant (Student's t test for significance of difference in proportions, P < 0 01)

Furthermore of those six dogs which showed arrhythmia under phosphate treatment the duration was shorter under treatment than in the recontrol test, to a highly significant degree (P <0 01) In the control studies a wide range of duration of arrhythmia was observed although four of the dogs showed a decrease in duration under phosphate treatment the degree of decrease in the treated group was not found to be significant.

The outstanding finding was that phosphate treatment prevented arrhythmia in more than half of the animals given digoxin up to a maximum predetermined dose.

LABORATORY FINDINGS The average changes in serum calcium potassium carbon dioxide and pH occurring during the two control experiments and the treated test are shown in Fig 3 These changes were not significant (P > 0 05) However a minor decrease in serum calcium was noted in the phosphate treated animals and the fall in pH and CO_2 was less marked

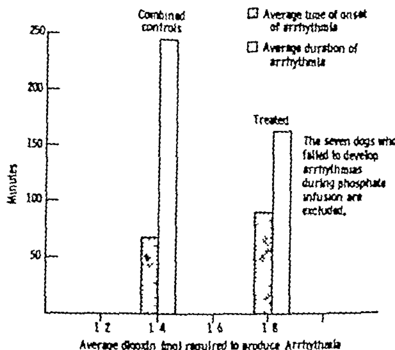


Fig 2. The average amount of digoxin required to produce arrhythmia as well as time of onset and duration of the rhythm irregularity in the control and treated experiments are shown. The differences are statistically significant (see text).

in the treated dogs. In four dogs the serum magnesium levels were measured before and after the three tests, but in none of the animals was a significant change observed. In three dogs inorganic phosphorus was measured before and after each test and no significant change was noted indicating that the plasma concentration of the phosphate per se did not influence the results.

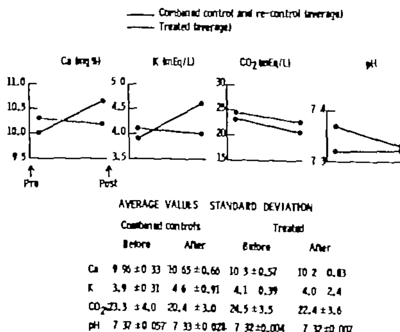
TYPE OF ARRHYTHMIA. The type of arrhythmia noted in each animal during the three experiments is described in Table I Seven of 13 dogs maintained normal sinus rhythm (NSR) when treated with inorganic phosphate, but all animals developed arrhythmias during the 26 control and recontrol experiments. Fig 4 demonstrates the occurrence of arrhythmias in one animal during the two control experiments and the persistence of NSR during the treated test.

Discussion

The mortality rate of dogs receiving progressive increments of intravenous digoxin until the onset of arrhythmia or up to 0 1 mg per kilogram of body weight was 0 per cent when treated with phosphate compared to 23.3 per cent in the untreated experiments. Arrhythmias developed in only 46 per cent of the dogs protected by phosphate infusions but appeared in all animals in the control or recontrol studies. If an arrhythmia occurred during the treated experiment an average of 0 41 mg or 30 per cent more of digoxin (total doses) was required to produce it. In these animals, the average duration of arrhythmia was 60 minutes, or 27 per cent shorter when treated with phosphate and the onset of arrhythmia was delayed an average of 21 minutes or 30 per cent.

The data in Fig 1 suggest that if the treated animals had been given the same dose of digoxin as in the control and recontrol experiment, the phosphate buffer might have prevented the development of arrhythmia in all dogs with one exception (dog H 197 recontrol test)

The mechanism of action of inorganic



AVERAGE VALUES STANDARD DEVIATION

	Combined controls		Treated	
	Before	After	Before	After
Ca	9 96 ±0 33	10 65 ±0.66	10 3 ±0.57	10 2 0.83
K	3.9 ±0 31	4 6 ±0.91	4.1 0.39	4.0 2.4
CO_2	23.3 ±4.0	20.4 ±3.0	24.5 ±3.5	22.4 ±3.6
pH	7 37 ±0 057	7 33 ±0 021	7 32±0.004	7 32±0 007

Fig 3 The average changes with the standard deviations of serum calcium potassium, CO_2 and pH prior to the administration of digoxin and at the end of the experiments in the two control and the treated periods are compared. The observed change in average level between treated and combined control tests was not significant (Student t test for significance of difference, $P > 0\ 05$) for any of the four clinical measurements.

Table I. Type of arrhythmia

Dog No.	Control	Treated	Re-control
H 298	Ventricular tachycardia (1.3 mg. digoxin/more than 250 min.)	Ventricular tachycardia (1.8 mg. digoxin/210 min.)	Ventricular tachycardia (1.1 mg. digoxin/dog died 5 min. after onset of arrhythmia.)
H-404	Atrial tachycardia at rate of 230/min. (1.5 mg. digoxin/235 min.)	Sinus tachycardia at a rate of 135/min. (1.9 mg. digoxin/—)	Ventricular tachycardia (1.8 mg. digoxin/more than 320 min.)
H 199	NSR with frequent runs of ventricular tachycardia (1.5 mg. digoxin/195 min.)	Ventricular tachycardia (1.8 mg. digoxin/110 min.)	A-V dissociation with idionodal rhythm and altered ventricular conduction. (1.7 mg. digoxin/more than 310 min.)
H 192	Atrial tachycardia at rate of 220/min. with altered ventricular conduction in form of trigeminy and quadrigeminy (1.5 mg. digoxin/75 min.)	Sinus arrhythmia with occasional S-A block (1.9 mg. digoxin/65 min.)	Ventricular tachycardia (1.9 mg. digoxin/more than 325 min.)
H 249	NSR with frequent S-A block (0.6 mg. digoxin/50 min.)	A-V dissociation with idionodal rhythm and altered ventricular conduction (1.4 mg. digoxin/240 min.)	Nodal rhythm (1.0 mg. digoxin/285 min.)
H 195	Marked sinus arrhythmia with frequent S-A block (1.1 mg. digoxin/50 min.)	NSR with beats of altered ventricular conduction in form of bigeminy (2.0 mg. digoxin/180 min.)	Ventricular tachycardia (1.9 mg. digoxin/more than 345 min.)
G-916	A-V dissociation with idionodal rhythm and altered ventricular conduction (1.6 mg. digoxin/315 min.)	NSR (2.0 mg. digoxin/—)	Ventricular tachycardia (1.7 mg. digoxin/more than 70 min.)
H-408	Ventricular tachycardia (1.9 mg. digoxin/more than 60 min.)	NSR (2.2 mg. digoxin/—)	Sinus arrhythmia with occurrence of A-V block (1.7 mg. digoxin/65 min.)
H 151	Ventricular tachycardia (1.7 mg. digoxin/285 min.)	A-V dissociation with idionodal rhythm and altered ventricular conduction (2.0 mg. digoxin/more than 185 min.)	A-V dissociation (1.6 mg. digoxin/300 min.)
G-963	Nodal tachycardia (1.0 mg. digoxin/more than 300 min.)	NSR (1.8 mg. digoxin/—)	A-V dissociation with idionodal rhythm and altered ventricular conduction. (1.2 mg. digoxin/more than 180 min.)
528	A-V dissociation with idionodal rhythm and altered ventricular conduction (1.2 mg. digoxin/15 min.)	NSR (1.2 mg. digoxin/—)	Ventricular tachycardia (1.0 mg. digoxin/dog died 100 min. after onset of arrhythmia)
691	Ventricular tachycardia (1.4 mg. digoxin/240 min.)	NSR (1.7 mg. digoxin/—)	Ventricular tachycardia (1.5 mg. digoxin/dog died 80 min. after onset of arrhythmia)*
511	A-V dissociation with idionodal rhythm and altered ventricular conduction (0.7 mg. digoxin/140 min.)	NSR (1.2 mg. digoxin/—)	A-V dissociation with idionodal rhythm and altered ventricular conduction (1.1 mg. digoxin/110 min.)

The first figure in parentheses represents the amount of digoxin in milligrams administered, and the second the duration of the arrhythmia in minutes. Seven dogs remained in an essentially normal sinus rhythm (NSR) throughout the treated experiments.

*Animal received 0.9 per cent saline infusion instead of 5 per cent dextrose.

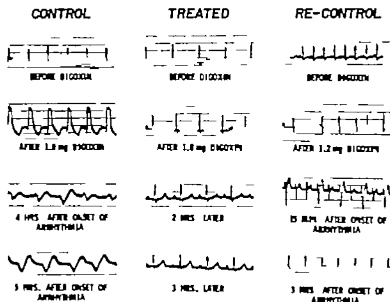


Fig. 4. The development of arrhythmias during the two control experiments (Dog No. G-968) and the persistence of NSR during the phosphate treated test are shown, despite the administration of a significantly greater amount of digoxin.

phosphate upon digoxin tolerance is not clear. The fact that the plasma calcium and pH were statistically the same in the treated and control experiments excludes changes of molecular calcium as an explanation for the increased digoxin tolerance. However, the possibility exists that a change in ionized extra- and intracellular calcium could alter myocardial irritability and be in part responsible for the increased digitalis tolerance observed. It has been demonstrated that calcium-chelating agents have relaxation activity proportionate to their ability to chelate calcium.[19] This may be due to an increase in intracellular potassium. Toda and West found in sinoatrial nodal pacemaker cells from rabbits, that ouabain toxicity was either prevented or delayed under conditions of low calcium but occurred earlier and at lower ouabain concentrations if calcium was raised.

It is not likely that correction of respiratory acidosis by the phosphate buffer played any role in increasing digitalis tolerance since eight dogs failed to show a change in CO_2 and pH during one of the control experiments and during the corresponding treated test but increased digitalis tolerance persisted when phosphate infusion was given. No significant difference in digitalis tolerance was observed when 0.9 per cent saline was infused instead of 5 per cent dextrose. It is unlikely that digitalis tolerance in the control experiments was decreased by infusion of 5 per cent dextrose, since no fall in potassium or phosphate could be observed. It does not seem likely that changes in serum potassium, magnesium or phosphate are responsible for the altered digitalis tolerance since differences in the serum levels of these ions were insignificant in the treated and untreated groups.

The absence of side effects of phosphate infusions in man, documented by Goldsmith and Ingbar,[17] and the lack of negative inotropic action suggest that the use of inorganic phosphate buffer may be helpful in the treatment of digitalis induced or arrhythmias in man if induced slowly in amounts not resulting in a sudden fall of serum calcium.

Summary

Digitalis tolerance was significantly increased and digoxin mortality markedly decreased by infusion of 0.1M disodium

monopotassium phosphate in dogs. The possible mechanism of phosphate protection is discussed

We are indebted to Dr Isabel Mountain for the statistical analyses of our data and to Mr Albert DaSilva for technical assistance.

REFERENCES

1. Withering W An account of the foxglove London 1785. Reprinted Medical Classics, Baltimore, 1937-8, The Williams & Wilkins Company ol. 2.
2. Cohen, B M Digitalis poisoning and its treatment, New England J Med. 246:225 1952.
3. *Roberts, J Ryuta, J Reilly J and Calrola,* V I fluence of reserpi and β TM 10 on digitalis-induced ventricular arrhythmias, Circulation Res. 13 149 1963
4. Grindell, E. H and Johnson, J R. Oestrogen protection against acute digitalis toxicity in dogs, N ture 190 1117 1961
5. Corday E. and Skelton R. B T The use of citrate salts for testing digitalis-induced cardiac arrhythmias in the experimental animal, Am. Heart J 67:237 1964
6. Barika, V Lang T W Pappelbaum, S., and Corday E Ajmalin, rauwolfia alkaloid for the treatme t of digitoxic arrhythmias, Am. J Cardiol 17:227 1966.
7. Mosley L nd Tyler M D The effect of diphenylhyda tion sodium (Dilantin) procain hydrochloride, procainamide hydrochloride and q inidine hydrochloride upon ouabain-induced ventricular tachycardia in the unanesthetized dog, Circulation 10:65 1954
8. Szekely P Jackson, F Wynne, N A., Vohra, J K. Batson, G. A., nd Dow W I Clinical observations on the use of propranolol in disorders of cardiac rhythm, Am. J Cardiol. 18:426, 1966.
9. Turner J R. B. Propranolol in the treatment of digitalis-induced and digitalis-resistant tachycardias, Am. J Cardiol. 18:450, 1966.
10. Epstein, S. E., and Braunwald, E. Beta-adrenergic receptor blocking agents, New England J Med., 271 1106, 1966 275 1175 1966.
11. *Cohen, S., Weissler A. M., and Shoenfeld,* C. D Antagonism of the contractile effect of digitalis by EDTA in the normal human ventricle Am. Heart J 69:502 1965.
12. Goldsmith, R. S. and Ingbar S. H. Inorganic phosphate treatment of hypercalcemia of diverse etiologies, New England J Med. 274:1 1966.
13. Ebashi, S., Ebashi, F and F jie, Y The effect of EDTA and its analogues on glycerinated muscle fibers and myosin adenosinetriphosphatase J Biochem. 47:54 1960.
14. Toda, N and West, T C. Modification by sodium and calci m of the cardiotoxicity induced by ouabain, J Pharmacol. & Exper Therap. 151:239 1966.

Case reports

A case of complete AV block produced by guanethidine

A previously undescribed side effect

H. J. L. Griffiths, M.B., B.S., M.R.C.S., L.R.C.P.
London, England

Guanethidine was introduced for clinical trials for the treatment of hypertension in 1959. Then as now its action was not fully understood but it appears that it inhibits the peripheral sympathetic nervous system selectively without affecting the parasympathetic system. It interferes with the normal release of transmitter substances (adrenergic catecholamines) at the postganglionic neuromuscular junction. The effect of this is to inhibit the vasoconstrictor action of the cathecholamines and also its excitatory action on the heart muscle and the bundle of His.

Although there have been many reports of bradycardia, not a single case of proved heart block has appeared in the literature. This is a case history of a patient who developed heart block on therapeutic doses of guanethidine and an attempt is made to show that this is not coincidental.

Case report

G. W., 65 years old, was a hypertensive patient of moderate degree who had been investigated and treated by this hospital from 1952. Various forms of therapy included reserpine, methyldopa, and guanethidine, but she had not persevered with any of these because of side effects. Six months prior to admission, she had been given methyldopa; at the time she said that she felt as if she might die. Her general practitioner noticed that her pulse rate was very slow and stopped the drug. Unfortunately, we have no further information about this episode.

She was admitted to this hospital for stabilization of her hypertension in November 1965. On examination, the pulse rate was 72 beats per minute and regular; blood pressure was 180/115 and clinically the heart was minimally enlarged. Fundi were Grade II, AV nipping being prominent. No other abnormalities were found.

Investigations showed a normal blood picture (hemoglobin 91 per cent) and electrolytes; blood urea was 32 mg/100 ml. and an intravenous pyelogram showed a hydronephrotic left kidney (as in 1952), the right kidney being normal. Urinary VMA† were also normal, and the electrocardiogram (ECG) was as shown in Fig. 1.

It was decided to try guanethidine once again, using the rapid-dosage calibration through progressively increasing intramuscular injections.

The patient was given 50 mg. of oral guanethidine daily. On November 12 and 17, the patient complained of dizzy spells. On examination, a regular bradycardia of 52 was found; an ECG confirmed heart block (Fig. 2). The guanethidine was stopped and the patient given sustained-action isoprenaline in steadily increasing dosage.

Serial ECGs taken over the course of the next 21 days up to December 6 show a gradual return to normal through various stages of heart block (Fig. 3). The isoprenaline was then eliminated without ill effect and the patient has since remained well. Her blood pressure readings are now about 180/110 and a recent ECG is the same as the original one.

From the Department of Radiodiagnosis, Hammersmith Hospital.
Received for publication May 8, 1967.
*Formerly senior house officer, Brook General Hospital, London.
†3-Methoxy-4 Hydroxy Mandelic Acid (V. M. A.)

Fig. 1 ECG taken on November 9, 1965 showing T-w... in ersion ... AVF and S waves in Leads I and AVL ... ggest ... g le... tric ... lar ischemia ... th possibly an ... omplet ... right bundle branch block.

Fig. 2 ECG taken on November 17, 1965 complete A V dissociation is present.

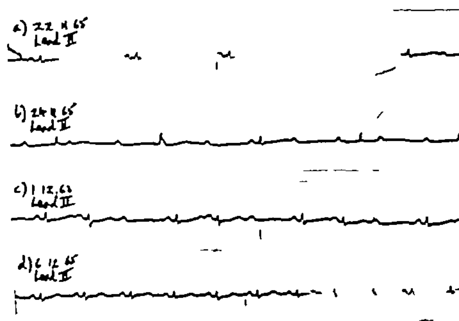


Fig. 3. Rhythm leads taken over the course of three weeks. a, November 22, 1965, shows two to one block; b, November 24, 1965, shows high grade A-V block; c, December 1, 1965, shows three to two block; d, December 6, 1965, shows return to sinus rhythm.

Discussion

Any drug which blocks the postganglionic sympathetic fibers must be expected to produce a variety of side effects and guanethidine is no exception. On the whole, its side effects are not incapacitating and they are probably all due to unopposed action of the parasympathetic nervous system. Those most frequently mentioned include postural hypotension, syncope, bradycardia, diarrhea, and fluid retention.

Taylor and associates[12] ascertained the effects of intravenous guanethidine on the systemic and pulmonary circulations of both normotensive and hypertensive subjects and found that although the majority of their patients had no significant change in pulse rate, two patients had marked changes. The first developed bradycardia and the second had a tachycardia. The authors commented that on a combination of exercise and guanethidine both groups of subjects experienced a drop in pulse rate.

Bradycardia was reported in two other series[8] and out of 63 patients investigated by Lewis and Kavelman 1963, one patient developed a pulse rate below 50. On the other hand, one patient with established heart block experienced no change in rhythm and a second patient with total atrioventricular dissociation remained in the same rhythm.

Bauer and associates[2] in 1961 had one patient with hypertensive heart failure who developed sinus bradycardia with nodal escape, and the authors suggested that special care should be taken with patients who were already receiving digitalis or diuretics. This comment was supported by Dollery and associates[4] in 1961 who showed that although bradycardia was common, it only gave rise to anxiety when the patient was digitalized. They described one patient who developed a bradycardia of 35 beats per minute but the heart block was not proved and on cessation of digoxin her pulse rate was increased to over 60 beats per minute.

Frohlich and Fries[5] in 1959 found that while the patient was sitting up the pulse rate was normal, but if he was placed in a supine position while receiving guanethidine the pulse rate dropped to between 65 and 44 beats. The authors postulate that this was due to unopposed parasympathetic activity. Finally, Sheppard and Zimmerman[11] (1959), in some of the original work

performed on guanethidine, found a 40 per cent reduction in the cathecholamine concentration in the blood vessels and in the heart. In 1960 Barnett and associates[1] postulated a reduced reflex sympathetic activity because of this and clinically this could be ascertained by exaggerated postural hypotension as well as an impaired cardio-accelerator response to exercise.

The etiology of the transient episode of the heart block in our own patient must be considered. Although our patient had an enlarged heart with electrocardiographic evidence of left ventricular ischemia she had not received either digitalis or diuretics, and had never been in heart failure. At the time of this episode, she was receiving no other drugs than from guanethidine and the heart block occurred five days after she had received the first dose of guanethidine. This is the normal accepted time interval before guanethidine is thought to start acting When the abnormal rhythm occurred the guanethidine had stopped and treatment with isoprenaline resulted in return to normal rhythm three weeks later

It is possible that in a profound attack of postural hypotension the patient might have had a myocardial infarction or alternatively that the underlying ischemic heart disease had made the conduction system unduly sensitive to guanethidine. This drug is thought to inhibit the excitatory action of cathecholamines on the bundle of His and an exaggerated effect of this type might be expected to result in a heart block. It is of interest that the patient suffered a similar episode of bradycardia while taking methyldopa and it is likely that the same mechanism was responsible e.g unopposed parasympathetic nervous system activity on the heart itself We attribute the three weeks delay before normal rhythm returned to the relatively slow excretion of the large oral and intramuscular doses of guanethidine.

It is surprising that although bradycardia has been frequently reported this is the first case of heart block to be reported during guanethidine therapy It would be of great interest to perform repeated ECG s on patients who develop bradycardia while receiving this drug in an attempt to ascertain the true incidence of heart block in patients taking guanethidine

Summary

A patient is described who developed complete A V block while receiving therapeutic doses of guanethidine. A brief survey is made of the incidence of bradycardia following therapy with guanethidine and we attempt to show that our patient may fit into this group

My thanks are due especially to Drs. W E. Mahon M Zoob, and O'Brien of Ciba who was kind enough to scrutinise world literature on the side effects of guanethidine.

REFERENCES

1 Barnett, A. J Kincaid-Smith, P and Simpson, F O Observations on a new hypotensive drug—guanethidine ("Ismelin") Med. J Australia 47:617 1960.
2. Bauer G. E., Croll, F J Goldrick R B., Jeremy D Rafton, J Whyt H. M and Young A. A. Guanethidine in treatment of hypertension, Brit. M J 5219:410. 1961
3 Blanshard, G and Essigman, W Guanethidine and hydrochlorothiazide in the treatment of hypertension, Lancet 2:334 1961
4 Dollery C. T Emslie-Smith, D and Shillingford, J P Haemodynamic effects of guanethidine, Lancet 2:331 1961
5 Frohlich E. D and Fries, E D Clinical trial of guanethidine, M. Ann. District of Columbia 28:419 1959
6 Leishman, A. W Matthews, A. L et al Guanethidine—hypotensive drug with prolonged action, Lancet 2 1044, 1959
7 Leishman, A. W and Sandler G. Hastening the control of blood pressure by guanethidine, Lancet 1:668, 1965.
8. Lewis, J A., Kavelman, D A.: Long-term follow-up of patients with hypertensive disease treated with guanethidine Canad. M A. J 88 1010, 1963.
9 Page, I H., Hurley R. E., and Dustan, H P The prolonged treatment of hypertension with guanethidine J A. M A. 175:543 1961
10. Pigeon, G D vignon, J Baron, P Trudel, J Default, C., and Genest, J Guanethidine administration in 28 hypertensive patients, Canad. M A. J 83:690, 1960.
11. Sheppard, J T and Zimmerman, J: Effect of guanethidine on tissue catecholamines, Pharmacologist, 1:69 1959
12. Taylor S. H., and Donald, K. W The circulatory effects of bretylium tosylate and guanethidine, Lancet 2:389 1960.
13. Taylor S. H Sutherland, G. R., Hutchison, D C., Kidd, B. S Robertson, P C., Kennelly B. M and Donald, K. W: The effects of intravenous guanethidine on the systemic and pulmonary circulation in man, Am Heart J 63:239 1962.
14. Wagener K. Retinal vascular changes in hypertension, Ann. I t. Med. 4:222 1930.

Familial Ebstein's anomaly of the tricuspid valve

Charles C Donegan Jr M.D
Marcus M Moore, M.D
Thomas M Wiley Jr M.D
Francisco A Hernandez M.D
*J Russell Green Jr M.D****
*Gerald L. Schiebler M.D*****
Miami Fla

Although familial occurrence of many congenital cardiac anomalies is well known,[1-4] it has not been reported in Ebstein's anomaly of the tricuspid valve. Previous reports have documented this tricuspid valve anomaly in one family member and other forms of congenital heart disease, particularly mitral valve malformations, in a different member. This report is concerned with a six year-old boy and his maternal uncle, both of whom had Ebstein's malformation and includes studies of other family members (Fig 1)

Case reports

Case 1 The propositus, a 6-year-old boy had been completely asymptomatic until five years of age, at which time his mother noted periodically that "his heart wasn't beating right. On palpating his chest, she described it as "feeling two or three hearts beating at the same time. Following several such episodes, the child was taken to a physician who detected a murmur A electrocardiogram (ECG) gave abnormal results and in one instance showed a supraventricular tachycardia. He was then admitted to the University of Florida Medical Center on Dec 1 1965 for further evaluation

This six year-old boy was light skinned, with reddish-brown hair and many freckles. He was in the sixtieth percentile for height and the seventy-fifth percentile for weight for his age group. A small, capillary hemangioma was under the left side of the chin. His fingers were t bby Cyanosis was not apparent. Venous pulsations in the neck were normal as were the peripheral arterial pulses. There was slight left precordial chest prominence. The maximal cardiac thrust was in the midclavicular line in the fifth left intercostal space. The first, second, and third heart sounds were all easily palpable, with the third sound being most prominent in the midclavicular line in the fourth left intercostal space. On auscultation the components of the first sound were widely split, with the second component louder than the first component in all areas. A grade 2/6 early decrescendo, systolic murmur as maximal in the third and fourth left intercostal space t the sternal border The second sound was widely split (0 06 second). Its components were of normal intensity and moved conventionally with respiration. The components of both the first and second sounds were "metallic in quality particularly the second component of the first sound. An accentuated third sound, heard best at the lower left sternal border and pex, as accompanied by a short middiastolic rasping murmur A low intensity fourth sound was noted in the midclavicular line in the fifth left intercostal space and at the apex At times t also

From the Children Clinic, Fort Myers, the University of Miami Medical School, Miami, and the University of Florida, Gainesville Fla

Supported by grants from the Florida Heart Association and its affiliated chapters, the Northeast Florida, Sarasota, and Palm Beach and Martin County Heart Associations, Developmental Physiology Training Grant Ty-HD-44, and the Cardiovascular Training Grant 5T1-HE-5443-01.

Received for publication May 18, 1967

*Children Clinic, Fort Myers, Fla.
**National Children Cardiac Hospital, University of Miami Medical School, Miami, Fla.
***Department of Medicine, University of Florida, Gainesville, Fla
****Department of Pediatrics, University of Florida, Gainesville, Fla. (Address communications to Dr Schiebler.)

performed on guanethidine found a 40 per cent reduction in the cathecholamine concentration in the blood vessels and in the heart. In 1960 Barnett and associates[1] postulated a reduced reflex sympathetic activity because of this and clinically this could be ascertained by exaggerated postural hypotension as well as an impaired cardio-accelerator response to exercise.

The etiology of the transient episode of the heart block in our own patient must be considered Although our patient had an enlarged heart with electrocardiographic evidence of left ventricular ischemia she had not received either digitalis or diuretics, and had never been in heart failure At the time of this episode she was receiving no other drugs than from guanethidine and the heart block occurred five days after she had received the first dose of guanethidine This is the normal accepted time interval before guanethidine is thought to start acting When the abnormal rhythm occurred the guanethidine had stopped and treatment with isoprenaline resulted in return to normal rhythm three weeks later

It is possible that in a profound attack of postural hypotension the patient might had a myocardial infarction or alternatively that the underlying ischemic heart disease had made the conduction system unduly sensitive to guanethidine. This drug is thought to inhibit the excitatory action of cathecholamines on the bundle of His and an exaggerated effect of this type might be expected to result in a heart block. It is of interest that the patient suffered a similar episode of bradycardia while taking methyl dopa and it is likely that the same mechanism was responsible e.g unopposed parasympathetic nervous system activity on the heart itself We attribute the three weeks delay before normal rhythm returned to the relatively slow excretion of the large oral and intramuscular doses of guanethidine.

It is surprising that although bradycardia has been frequently reported this is the first case of heart block to be reported during guanethidine therapy It would be of great interest to perform repeated ECG s on patients who develop bradycardia while receiving this drug in an attempt to ascertain the true incidence of heart block in patients taking guanethidine.

Summary

A patient is described who developed complete A V block while receiving therapeutic doses of guanethidine. A brief survey is made of the incidence of bradycardia following therapy with guanethidine and we attempt to show that our patient may fit into this group

My thanks are due especially t Drs. W E. Mahon, M Zoob, and O'Brien of Ciba who was kind enough to scrutinise world literature on the side effects of guanethidine.

REFERENCES

1 Barnett, A. J Kincaid-Smith, P and Simpson, F O Observations on a new hypotensive drug—guanethidine ("Ismelin") Med. J Australia 47:617 1960.
2. Bauer G. E. Croft, F I Goldrick, R. B., Jeremy D Rafton, J Whyte, H M and Young, A A. Guanethidine in treatment of hypertension, Brit. M J 5219:410, 1961
3 Blanshard G and Eangman, W Guanethidine and hydrochlorothiazide in the treatment of hypertension, Lancet 2:334 1961
4 Dollery C. T Emslie-Smith D and Shillingford J P : Haemodynamic effects of guanethidine Lancet 2:331 1961
5 Frohlich, E. D and Fries, E D Clinical trial of guanethidine, M Ann. District of Columbia 28:419 1959
6 Leishman, A. W Matthews, A. L. et I Guanethidine—hypotensive drug with prolonged action, Lancet 2 1044, 1959
7 Leishman, A. W and Sandler G.: Hastening the control of blood pressure by guanethidine Lancet 1:668, 1965
8. Lewis, J A. Kavelman, D A.: Long-term follow-up of patients with hypertensive disease treated with guanethidine, Canad. M A. J 88 1010 1963.
9 Page, I H. Hurley R. E., and Dustan, H P The prolonged treatment of hypertension with guanethidine, J A. M A. 175:543, 1961
10. Pigeon, G Davignon, J Biron, P Trudel, J Default, C., and Genest, J : Guanethidine administration in 28 hypertensive patients, Canad. M A. J 83:690, 1960.
11. Sheppard J T and Zimmerman, J : Effect of guanethidine on tissue catecholamines, Pharmacologist, 1:69 1959
12. T ylor S H., and Donald, K. W The circulatory effects of bretyli m tosylate and guanethidine, Lancet 2:389 1960.
13 T ylor S. H. Sutherland, G. R., Hutchison, D C., Kidd, B. S Robertson, P C. Kennelly B. M nd Donald, K. W : The effects of I travenous guanethidine on the systemic and pulmonary circulation I man, Am Heart J 63:239 1962.
14 Wagener K. Retinal vascular changes in hypertension Am. I t. Med. 1:222, 1930.

Familial Ebstein's anomaly of the tricuspid valve

Charles C Donegan Jr M D
Marcus M Moore M.D
Thomas M Wiley Jr M.D
Francisco A Hernandez, M.D **
J Russell Green Jr M.D
Gerold L. Schiebler M.D ****
Miami Fla

Although familial occurrence of many congenital cardiac anomalies is well known,[1,3] it has not been reported in Ebstein's anomaly of the tricuspid valve. Previous reports have documented this tricuspid valve anomaly in one family member and other forms of congenital heart disease, particularly mitral valve malformations, in a different member. This report is concerned with a six year-old boy and his maternal uncle both of whom had Ebstein's malformation and includes studies of other family members (Fig 1)

Case reports

Case 1 The propositus, a 6-year-old boy had been completely asymptomatic until five years of age, at which time his mother noted periodically that "his heart wasn't beating right." On palpating his chest she described it as "feeling two or three hearts beating at the same time." Following several such episodes, the child was taken to a physician who detected a murmur. An electrocardiogram (ECG) gave abnormal results and in one instance showed a supraventricular tachycardia. He was then admitted to the University of Florida Medical Center on Dec. 1 1965 for further evaluation

This six year-old boy was light skinned, with reddish-brown hair and many freckles. He was in the sixtieth percentile for height and the seventy-fifth percentile for weight for his age group. A small, capillary hemangioma was under the left side of the chin. His fingers were stubby. Cyanosis was not apparent. Venous pulsations in the neck were normal as were the peripheral arterial pulses. There was a slight left precordial chest prominence. The maximal cardiac thrust was in the midclavicular line in the fifth left intercostal space. The first, second, and third heart sounds were all easily palpable, with the third sound being most prominent in the midclavicular line in the fourth left intercostal space. On auscultation the components of the first sound were widely split, with the second component louder than the first component in all areas. A grade 2/6 early decrescendo, systolic murmur was maximal in the third and fourth left intercostal space at the sternal border. The second sound was widely split (0 06 second). Its components were of normal intensity and moved conventionally with respiration. The components of both the first and second sounds were metallic in quality particularly the second component of the first sound. An accentuated third sound, heard best at the lower left sternal border and apex, was encompassed by a short middiastolic rasping murmur. A low intensity fourth sound was noted in the midclavicular line in the fifth left intercostal space and at the apex. At times it also

From the Children's Clinic, Fort Myers the University of Miami Medical School, Miami and the University of Florida Gainesville Fla
Supported by grants from the Florida Heart Association and its affiliated chapters, the Northeast Florida, Suncoast, and Palm Beach and Martin County Heart Associations, Developmental Physiology Training Grant, T1-HD-5 and the Cardiovascular Training Grant 5T 1HE-5493-05
Received for publication May 10, 1967
*Children's Clinic Fort Myers, Fla
**Variety Children's Cardiac Hospital, University of Miami Medical School, Miami, Fla.
***Department of Medicine University of Florida, Gainesville, Fla.
****Department of Pediatrics, University of Florida, Gainesville, Fla. (Address correspondence to Dr. Schiebler)

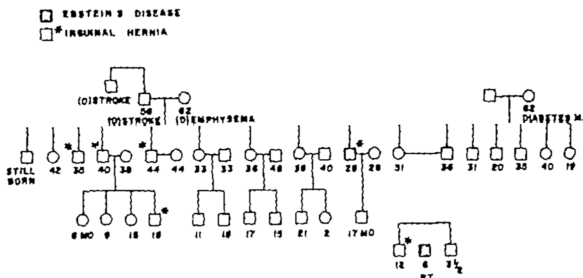


Fig. 1. Pedigree of family with Ebstein anomaly. Propositus is the 6-year-old boy. He and his maternal uncle are indicated by the cross-hatching. Note the high incidence of inguinal hernia (indicated by asterisks) occurring in male members of the same family.

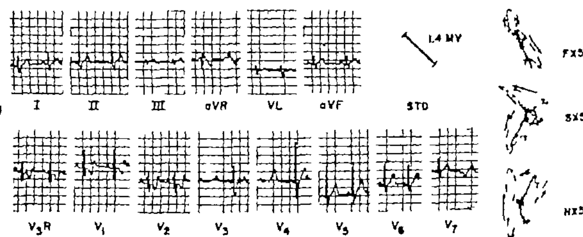


Fig. 2. Electrovectorcardiogram in 6-year-old boy with Ebstein's anomaly (Grishman cube technique). Precordial Lead V1 shows peaked P waves indicating right atrial enlargement. Note the splintered QRS complex in the right precordial leads, the pattern suggesting right ventricular volume overload. The vectorcardiogram shows an enlarged P loop directed slightly leftward, inferior and anterior consistent with right atrial enlargement. The abnormal T wave is directed leftward, inferior and equal anterior and posterior producing diphasic T waves in the right precordial leads.

was encompassed by a short low intensity diastolic murmur. The remainder of the physical examination was normal.

Routine blood and urine studies were normal. The ECG (Fig. 2) revealed right atrial enlargement, normal atrioventricular conduction and an rsR' pattern in V1 with normal left ventricular activity. QRS voltages in the standard and augmented limb leads were lower than normal.

Chest roentgenograms showed a normal over-all heart size but no distinct main pulmonary artery segment. Increased right border convexity suggested right atrial enlargement. The pulmonary vasculature was normal (Fig. 3).

Cardiac catheterization studies showed mild elevation of right atrial pressure (8/2 mm. Hg), with the "a" wave being predominant. The right ventricular pressure was 28/-2 to 3 and the pulmonary artery pressure was 22/12 mm. Hg. A concomitant right femoral artery pressure was 86/52 mm. Hg



Fig. 3. Thoracic roentgenogram of 6-year-old boy with familial Ebstein anomaly. The over-all heart size is normal. There is an increase in right heart border convexity suggesting right atrial enlargement. The main pulmonary artery segment is not seen, straight left border being present from the apex to the aortic shadow. The pulmonary vascular markings are normal. This contour is not infrequently seen in asymptomatic children with Ebstein anomaly.

There was no significant left-to-right shunt. The inferior vena ca dye curve, however, showed small initial early deflection, representing minute right-to-left shunt presumably through patent foramen ovale. The cardiac output (Fick technique) was normal (4.3 L. per minute), as were the calculated pulmonary and systemic bed resistances. The intracavitary ECG with simultaneous pressure tracings recorded the tricuspid valve location to be about 0.5 cm. to the left of the spine in the AP view. On continued withdrawal, there was an area in which the intracardiac ECG showed right ventricular potential concomitant with right atrial pressure. Such findings are diagnostic of Ebstein anomaly with attachment of significant portion of the tricuspid valve below the atrioventricular annulus. There were no complications of this procedure.

Since the patient had had no bouts of paroxysmal tachycardia during the previous four months, he was not placed on medication. The only admonition given was the avoidance of prolonged strenuous competitive sports.

CASE 2. The 29-year-old maternal uncle of the propositus was known to have heart trouble at birth. Cyanosis and digital clubbing had been present since at least five years of age.

At present, he owns a roofing company, and he often works alongside his employees. He is able to walk several blocks without undue exertion. However, he can run only short distances—less than 25 yards. He has had paroxysms of tachycardia, causing feelings of weakness, but has never fainted. The incidence of such episodes of tachycardia and his exercise tolerance have remained stable during the past decade. He denied equating chest pain, peripheral edema, but has noted that he has unusual photophobia. Even short exposures to sunlight cause undue eye irritation. He has never taken any cardiac medication.

The uncle was an asthenic man of medium height with marked cyanosis of the skin and mucous membranes, suffusion of the conjunctiva, and severe clubbing of the digits. Telangiectasia and diffuse ruddiness were particularly prominent over the cheeks, malar areas, and chin.

The blood pressure was 115/80 mm. Hg with the diastolic endpoint difficult to determine. The peripheral arterial pulses and neck venous pulses were normal. The chest contour was normal but the heart itself was very hypoactive. The maximal impulse was in the anterior axillary line in the sixth left intercostal space. The first heart sound was slightly diminished in intensity and was comprised of two main components split about 0.04 second. The second component had a clicking quality, particularly along the lower left sternal border. There it was followed by a grade 1/6 short decrescendo systolic murmur with superficial tonal qualities. The second sound was normal in intensity but consisted of only a single component in all areas. Along the lower left sternal border it was followed by a very prominent third sound equal in intensity to S_1. The third sound was followed by a delay and then accentuated fourth heart sound.

The hemoglobin was 20 Gm. and the hematocrit 77. The chest film showed surprisingly normal cardiac contour (Fig. 4), but the pulmonary artery trunk was not visible as a distinct segment. The peripheral pulmonary vasculature was distinctly less than normal.

An ECG (Fig. 5) showed right atrial enlargement, normal atrioventricular conduction and of the terminal right and superior



Fig. 4 Chest x-ray of 29-year-old ma with familial Ebstein anomaly. The cardiac contour is nonspecific and ould pass as normal. The lateral films suggest right heart enlargement. The peripheral pulmonary arterial vascularity appears less prominent than usual.

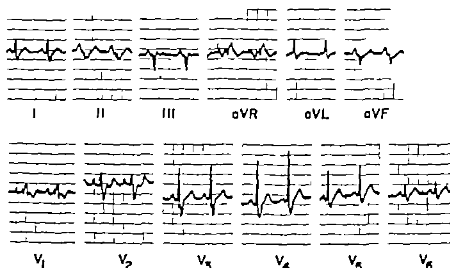


Fig. 5 An ECG of 29-year-old man with familial Ebstein anomaly. The P w ves, especially in Lead II are abnormally large and peaked indicating right trial enlargement. The QRS pattern is that of right bundle branch block with slow ng of the terminal rightward superior and predominat ly anterior QRS forces. There is diffuse low oltage of the QRS complexes in the standard and augmented limb leads and an rsR pattern n V

dominantly anterior QRS forces consistent with right bundle branch block. Left ventricular activity was normal.

Cardiac catheterization performed t 21 years of age, showed a very large right trium (in which the catheter could easily be coiled), and large right-to-left shunt t the atrial level. Pressures in the right atrium were 11/5 with the dominant wave being an " wave and in the right ventricle 25/5 mm. Hg. The pulmonary artery was not entered. The brachial artery saturation was 91 per cent. An intracavitary ECG pull-back tracing from the right ventricle to the right trium was again diagnostic of Ebstein's anomaly of the tricuspid valve, there being an area of right trial pressure concomitant with a right ventricular configuration on the i tracavitary ECG.

Remaining family members. Other tudies in this family included cardiac examination thoracic roentgenograms and ECG's in both parents and both male siblings of the propositus, as well his 17 month-old male cous (the son of the afflicted ncle). In each case, all studies ere normal.

Chromosomal analyses were performed upon the propositus, his mother and his maternal uncle. Leukocytes were cultured from their peripheral blood using a modification of the technique described by Genet and Anger.[3] A total of 30 cells were counted in each instance and were euploid. Idiograms revealed the chromosomes to be normal in size, shape and configuration.

Discussion

There are two reports of families in which one member had Ebstein's anomaly but the cardiac findings in the second case were not well documented. Grob and his associates[4] reported that a maternal cousin of the index case had cyanotic congenital heart disease and Blacket and associates[5] reported on a patient with Ebstein's malformation whose elder brother was known to have heart disease. This older sibling died suddenly at 17 years of age while playing tennis.

Later reports[6] emphasized that when one member of the family has Ebstein's anomaly another may have a lesion of the left side of the heart, particularly left atrioventricular valve insufficiency. Gouffault and Le Damany[6] noted a 3-year-old boy who at necropsy showed an Ebstein's type of tricuspid valve. A younger sister on the basis of clinical findings, was also thought to have Ebstein's anomaly. When this sister died at five years of age, however necropsy findings showed a parachute mitral valve deformity with the posterior inferior margin of the valve attached to the sides of the ventricle rather than the annulus. This deformity (left sided Ebstein's) may be considered the mitral valve counterpart of Ebstein's anomaly and is usually associated with congenitally corrected transposition. This malarrangement of the great vessels was not present in this latter case. Thus the authors[7] reinterpreted their findings as documenting classical Ebstein's anomaly of the tricuspid valve in one member of the family and in the other an analogous anomaly of the mitral valve.

Yamauchi and Cayler[9] reported on a patient with Ebstein's anomaly whose cousin had mitral regurgitation and congenitally corrected transposition of the great vessels. The latter combination usually means that the left atrioventricular valve has the Ebstein type of deformity.

Recently Sommer[10] documented a family in which the young son had Ebstein's anomaly of the tricuspid valve and the father idiopathic ventricular hypertrophy of the heart, particularly the left ventricle.

Summary

Ebstein's anomaly of the tricuspid valve has not been reported previously in two members of the same family. A 6-year-old boy and his 29-year-old maternal uncle are described both of whom had the Ebstein type of tricuspid valve documented by cardiac catheterization.

A review of the literature suggests that when multiple cases of congenital heart disease occur in a family in which one individual has Ebstein's malformation of the tricuspid valve, another member may have the same anomaly or even more likely an analagous anomaly of the left-sided atrioventricular valve with or without congenitally corrected transposition of the great vessels.

REFERENCES

1. Lamy M., de Grouchy J. and Schweisguth, O. Genetic and non-genetic factors in the etiology of congenital heart disease. A study of 1 188 cases, Am. J. Hum. Genet. 9 17 1957
2. Nora, J. J. and Meyer T. C. Familial nature of congenital heart diseases, Pediatrics 37:329 1966.
3. Genet, P. and Anger C. Observations on the technique for the study of human chromosomes by the culture of leukocytes from peripheral blood, Canad. M. A. J. 88:302, 1963
4. Grob, M. Bettex, M. and Rosen, E. Zur Diagnose des Morbus Ebstein, Helvet. paediat. acta 7:85, 1952.
5. Blacket, R. B., Sinclair Smith, B. C., Palmer A. J. Halliday J. H., and Maddox, J. K. Ebstein disease. A report of five cases, Australasian Ann. Med. 1:26, 1952.
6. Gouffault, J. and Le Damany L. Maladie d'Ebstein dans une même fratrie. Arch. mal. Coeur 49:664, 1956.
7. Gouffault, J. Le Damany L. and Lenegre, J. Un type particulier d'anomalie congénitale de la valve mitrale, Arch. mal. Coeur 53 1175 1960.
8. Schiebler G. L., Edwards, J. E. Burchell, H. B., DuShane, J. W. Ongley P. A., and Wood, E. H. Congenital corrected transposition of the great vessels. A study of thirty-three cases, Pediatrics 27:851 1961
9. Yamauchi, T. and Cayler G. G. Ebstein anomaly in the neonate. A clinical study of three cases observed from birth through infancy Am. J. Dis. Child. 10 163 1964.
10. Sommer L. S. Idiopathic ventricular hypertrophy of the heart, J. Florida M. A. 53 1173, 1966.

Medical and physiological considerations in the use of artificial cardiac pacing Part I*

Edward M. McNally, M.D.
Alberto Benchimol, M.D.
La Jolla, Calif., and
Phoenix, Ariz.

In the relatively few years since pacemakers have been introduced into clinical practice, a very large literature has accumulated on various aspects of their use. Adequate review of this literature is not possible in anything less than a monograph and will not be attempted here. Rather we will consider certain problems in connection with their use which have in our observation given rise to confusion among internists and cardiologists. These problems have been surprisingly physiological and medical rather than technical or surgical, and it is with the former that we will be principally concerned. To the extent that problems of the latter kind will be discussed they will be considered from the standpoint of their medical and physiological implications.

Particular attention will be given the question of indications for pacing, for this has in our experience been the greatest source of confusion.

Indications for using pacemakers

There are many uses to which pacemakers may be put, but in current clinical practice they are employed almost solely for the purpose of speeding the heart whose own rate is so slow that circulatory problems of one kind or another result. Such slowing is occasionally due to sinus node depression or to sinoatrial block, but in the vast majority of instances it is the consequence of advanced or complete atrioventricular (AV) block, and it is with this disturbance that we shall be almost exclusively concerned in this section.

It is well at the outset to review the definitions of these and other related arrhythmias, since the terms are often imprecisely used. First and most important, *block* must be distinguished from *interference*. Partial or complete failure of AV conduction occurs in both, but for quite different reasons. In block it is due to dysfunction of the AV conducting tissue; in interference it is due to physiological refractoriness of the conducting tissue induced by retrograde penetration of impulses from a second, usually faster pacemaker located in or below the AV node. In practice, conduction failure can be attributed to dysfunction of the con-

From Scripps Clinic and Research Foundation, La Jolla, Calif., and from Institute for Cardiovascular Diseases, Good Samaritan Hospital, Phoenix, Ariz.
Supported in part by grants from United States Public Health Service, National Heart Institute Nos. 4-F3-HE-1 [illegible] 660-02 and HF 5115-01, Arizona Heart Association and Southwest Foundation for Medical Research and Education.
*Part II of this study will appear in an early issue of the Journal.
Address: Scripps Clinic, La Jolla, Calif.

ducting system (i.e. to block) only if it cannot be explained by physiological refractoriness (i.e. by interference). Block is thus an exclusion diagnosis.

AV dissociation signifies that the atria and the ventricles are under the control of different pacemakers. A purely descriptive term, it implies nothing as to the underlying mechanism, which may be either block or interference or a combination of the two.

In *complete AV block* no atrial impulses reach the ventricles and complete AV dissociation is present, the ventricles being paced by a *subsidiary pacemaker* in or below the AV node. In *second-degree AV block* some impulses, but not fewer than every other, are conducted and the rest are blocked. Block in which the conduction ratio is 2:1 or less is referred to as *advanced AV block*. *High-degree* or *high-grade AV block* is a looser term encompassing both advanced and complete AV block, and *partial AV block* includes both second-degree and advanced AV block.

Second-degree AV block is of two kinds: *Mobitz Type I*, the common form, in which progressive PR prolongation precedes the blocked beat (Wenckebach phenomenon), and *Mobitz Type II*, a rare form, in which the PR interval is constant.[4] There are great differences between these two forms of block, and they are important for our discussion (Table I). Type I block usually occurs transiently in the course of an acute toxic or inflammatory process (especially digitalis poisoning and rheumatic fever) or in acute inferior infarction, and is associated with reversible conducting system pathology or none. Type II block,

Table I. Contrasting features of Mobitz Type I and Mobitz Type II second-degree AV block[4]

	Mobitz Type I	*Mobitz Type II*
Conducting system pathology	Usually none (functional) or reversible inflammation or edema	Usually extensive, irreversible disruption of conducting system; anatomic bilateral bundle branch block
Etiology	Acute myocarditis (especially rheumatic fever); acute intoxication (especially digitalis); acute diaphragmatic infarction; vagotonia	Usually idiopathic, degenerative(?) process; occasionally (usually partially) infarctional
Electrophysiological features		
1. Site of block	Junctional tissue between atrium and AV node	Bifurcation or below
2. AV conduction	Progressive PR prolongation precedes blocked beat (Wenckebach phenomenon)	PR interval stable
	Advanced AV block uncommon; 2:1 or 3:1 may occur, but Wenckebach periods usually present elsewhere in record	Advanced AV block commonly associated and is considered to be a form of Mobitz II
3. QRS	Usually normal duration	Usually prolonged to 0.12 sec. or beyond. Contour often that associated with bilateral bundle branch block
4. Location of subsidiary pacemaker	AV node	Below bifurcation
Course		
1. Duration	Usually transient event in course of acute process; rarely persistent	Usually persistent and/or recurrent
2. Relation to advanced or complete AV block	Infrequently progresses to high-grade block; when it does, latter usually transient	Very commonly progresses to persistent high-grade block

by contrast, is associated with severe and irreversible destruction of the conducting system and tends to persist or recur chronically. Mobitz Type I block infrequently progresses to high grade block and the latter, when it occurs, is usually transient. Mobitz Type II block, on the other hand, is so frequently associated with advanced and complete AV block that they are commonly considered to be different forms of the same disturbance.[2,3] The electrophysiological level of the block is high in the AV node in Mobitz Type I and at or below the bifurcation in Type II, so that if it should lead to dissociation, the subsidiary pacemaker is located in the AV node in Type I block and below the bifurcation in Type II block. The importance of this is that the characteristics of nodal and idioventricular pacemakers are very different. The former are relatively rapid, averaging 45 to 50, and stable, whereas the latter are slow, averaging 25 to 44, and unstable, tending to irregularity and unexplained arrest. Advanced or complete AV block arising from Type II block is thus a far more dangerous problem than high grade AV block arising in Type I block.

Thus, AV block may be considered as falling into two broad categories. That in the first category has the pathological and electrophysiological characteristics of Type I block as just described; it is usually transient, rarely progresses to high-grade AV block, and, when it does, is associated with a relatively rapid and stable ventricular rate. That in the second has the pathological and physiological characteristics of Mobitz Type II block; it tends to chronicity, very often leads to advanced and complete block, and, when it does, is usually associated with a slow and unstable idioventricular rhythm. Block of the first kind is thus ephemeral and in itself benign, whereas that of the second kind is persistent and malignant.

Finally, we must discuss the differential diagnosis of AV dissociation because lack of proper interpretation in this matter has invalidated much otherwise useful information on heart block. Persistent AV dissociation in which a normal or accelerated sinus rate coexists with a ventricular rate below 45 per minute is clearly due to block, since the continuous failure of AV conduction in such a case could not possibly be attributed to physiological interference. Similarly, dissociation in which a brisk ventricular rate is associated with an atrial rate roughly as fast, in which the cycle lengths do not greatly exceed the refractory periods in either chamber, and in which an occasional capture occurs is clearly due to interference. In such cases the cause of dissociation is obvious. Difficulties arise, however, when Mobitz Type I second-degree AV block coexists with normal or moderately accelerated nodal rates (50 to 70 per minute), particularly if the sinus rate is slow, for in this circumstance, a remarkably persistent and complete AV dissociation can occur *even if the AV block is quite mild in degree.* The latter combination of circumstances is of more than theoretical importance, for it occurs very often clinically, especially in digitalis poisoning and inferior infarction. It has very often been taken to represent "complete heart block" and classified as such, and this mislabeling has invalidated most of the statistics on the incidence of high-grade heart block in these two settings.

Advanced and complete AV block may be acute or chronic, transient or permanent, or intermittent or continuous, but it gives rise to only two types of circulatory disturbance. (1) By predisposing to certain arrhythmias, it may lead to precipitous drops in the cardiac output and episodic disturbances in consciousness, as in the Stokes-Adams syndrome. (2) It may, because of the slow ventricular rate with which it is usually associated, lead either to chronic circulatory insufficiency or to other arrhythmias. Pacemakers have a major role in all these situations.

1. *Chronic advanced or complete AV block with episodic disturbance of consciousness. The Stokes-Adams syndrome.*[2,4] The Stokes-Adams syndrome is the classic indication for using a pacemaker. This eponym has been variously defined,[1,12,13] but we shall use it here to refer to the syndrome of (1) recurrent attacks of unconsciousness with or without seizures (2) due to advanced or complete AV block or its complications and (3) occurring other than in the course of an acute illness or

intoxication. This somewhat restricted definition excludes high-degree block complicating acute myocardial infarction and similar syndromes associated with sinus bradycardia and sinoatrial block. The former is so much a problem unto itself that it will be discussed separately and the latter[4,29] so uncommon as to be beyond the scope of this review.

(AV block due to digitalis poisoning it will be noted is also excluded by this definition. Little is lost in consequence, however, for digitalis in amounts sufficient to cause significant AV block nearly always simultaneously accelerates a nodal subsidiary pacemaker so as to maintain the ventricular rate in excess of 50 per minute; the drug therefore rarely gives rise to paroxysmal disturbances in consciousness.[14,16] Most cases of digitalis-induced complete heart block are in fact instances of AV dissociation due to the concurrence of a slow atrial rate, Mobitz Type I second-degree AV block, and an acceleration of the nodal pacemaker to rates higher than 50 per minute. This is reflected in one series in which the average ventricular rate in "complete heart block" due to digitalis toxicity was 55 per minute as compared to one of 38 per minute in "idiopathic cases"; the diagnosis of complete heart block usually cannot be made in the presence of dissociation at a ventricular rate of 55 per minute. Pacing is thus rarely needed in digitalis-induced block, in which treatment consists rather in withholding the drug and avoiding the use of potassium since this ion will only further increase the block. When episodic disturbances in consciousness do occur in digitalis poisoning they are more likely the result of ventricular irritability and tachyarrhythmia than of block; in such cases, treatment should properly include the use of potassium and perhaps, a β-blocking agent.)

PATHOGENESIS OF CHRONIC ADVANCED AND COMPLETE AV BLOCK. The Stokes-Adams syndrome, though it occurs most often in the aged is usually not due to ischemic heart disease. Infarction or ischemia of conducting tissue is infrequently the sole cause of chronic AV block and is not even an important contributing one in more than a third of cases.[9,11,22,31,33] The reasons for this will become clear when AV block in acute myocardial infarction is discussed.

The underlying lesion in the great majority of patients with the Stokes-Adams syndrome is *anatomic bilateral bundle branch block*[22,31,37,39] due to degenerative fibrosis of both bundle branches or less often, the bifurcation. This lesion, which usually spares the AV node and the His bundle, is part of a more extensive sclerotic

Table II. Electrocardiographic manifestations of anatomic bilateral bundle branch block

I. AV conduction disturbance
- Complete AV block
- Advanced AV block[*] without evidence of Wenckebach conduction in long or repeated records
- Mobitz Type II AV block
- (Mobitz Type I AV block is not a manifestation of bilateral bundle branch block)

II. QRS conduction patterns (QRS widening nearly always present)[9,11,22,31,33,36,39]
- Masquerading bundle branch block[**,38] (CLBBB in limb leads and CRBBB in precordials)†
- *Alternating bundle branch block* (*Either in the same or different tracings, beats of both the LBBB and the RBBB type are present*)†
- CRBBB with left axis deviation[22,31,33,37]‡
- CRBBB with QRS > 0.14 second is often due to bilateral bundle branch block
- QRS > 0.12 second, whether the pattern suggests RBBB, LBBB or is of the "anomalous" or "atypical" intraventricular block type, should raise the possibility of anatomic bilateral bundle branch block and, in a patient with recurrent disturbance in consciousness, of the Stokes-Adams syndrome. The likelihood of bilateral bundle branch block is increased (1) if in addition, PR prolongation is present and (2) if the QRS is > 0.14 second

Abbreviations: CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block.
†In practice these patterns can be considered pathognomonic of bilateral bundle branch block.
‡This pattern is in about half of cases due to anatomic bilateral bundle branch block.

process involving primarily the contiguous skeleton of the heart most notably the pars membranosa the central fibrous body and the aortic ring. These degenerative changes are poorly understood but are believed due to the cumulative effects of mechanical wear and tear on these structures, for they increase with age and occur earlier and more severely in the presence of hypertension they do not appear to be related to ischemia.[illegible] The right bundle branch which takes a long course before ramifying tends to be more completely destroyed than the left, which ramifies high and diffusely[illegible] and this asymmetry results in an electrocardiographic predominance of right over left bundle branch block patterns in conducted beats in this syndrome[illegible] (Table II). The long course taken by the right bundle through the intraventricular septum renders it more vulnerable than the left also to infarction so that when bilateral bundle branch block is due in part to ischemia the infarctional component most often involves the right bundle.[illegible]

There are many other causes of advanced or complete AV block, but these are less frequently encountered. Disease of the aortic valve and ring particularly calcific aortic stenosis, is not an uncommon cause of bilateral bundle branch block and therefore of advanced and complete AV block.[illegible] Chagas disease,[illegible] though a very common cause of AV block in some parts of the world is rarely seen in temperate regions. Sarcoidosis[illegible] and the collagenoses[illegible] may occasionally produce AV block and, together with myocarditis and muscular dystrophy[illegible] account for an appreciable portion of cases in the young. Infiltrative processes such as amyloidosis, hemochromatosis,[illegible] and diphtheria[illegible] may also cause high-grade block, but are rare. Congenital heart block[illegible] usually does not of itself lead to difficulties, but may occasionally do so[illegible] even if unassociated with other lesions in such cases, however fatigability and poor exercise tolerance are much more often a problem than is episodic unconsciousness. Heart block complicating cardiac surgery[illegible] presents as an acute problem and it is especially common during repair of ventricular septal defect.

MECHANISMS OF SYNCOPE IN THE STOKES-ADAMS SYNDROME. Loss of consciousness, the hallmark of the Stokes-Adams syndrome results from a precipitous fall in cardiac output. Stable high grade AV block does not in itself directly bring this about but, by predisposing to both paroxysmal ventricular tachyarrhythmias and electrical asystole (Fig. 1) it does so indirectly.[illegible]

The tendency to ventricular tachyarrhythmia in high-grade AV block results from the concurrence of ventricular premature beats and a prolonged and delayed vulnerable phase of the ventricle. Ventricular premature beats are favored by the slow rate which "releases or unmasks" ectopic foci that would be suppressed by a faster rate. The delay and prolongation of the vulnerable phase results both from the bradycardia itself and from the slow and aberrant ventricular excitation and repolarization which is usually present and manifest by widened and bizarre QRST complexes. A run of tachyarrhythmia is set off when a ventricular premature beat falls into the vulnerable phase of the previous beat.[illegible] The slower the rate the more likely is this to occur. When a period of asystole is terminated by a burst of ventricular tachycardia or fibrillation—a common sequence of events during an attack—this is usually the mechanism the first escape beat being followed closely by an ectopic, which triggers the burst.

Electrical asystole may occur in several ways. In intermittent or unstable forms of AV block it may follow either the sudden appearance of high-grade block or a sudden marked increase in the degree of block as the result of retarded escape of the subsidiary pacemaker. In stable high-grade block the subsidiary pacemaker may for no apparent reason abruptly slow or stop altogether. It should be recalled that subsidiary pacemaker is located below the bifurcation in these cases and that it is a characteristic of pacemakers at this level—in contrast to those in the node—that they tend to retarded escape, slow and rather irregular rates, and unexplained arrest.[1]

Asystole may also follow the sudden cessation of a run of ventricular tachy-

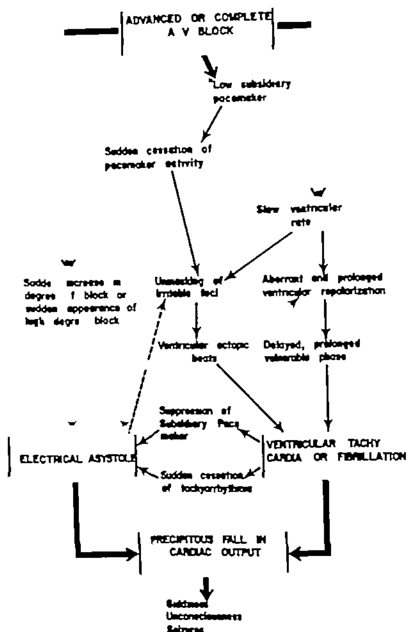


Fig 1 Mechanisms of precipitous fall in cardiac output in advanced or complete AV block

arrhythmia, where it results from rapid rate having suppressed the subsidiary pacemaker. In tl s latter and very common sequence of events the fall n output is more often due to the asystole than to the tachyarrhythmia which preceded and produced it

I th Stoke Adams syndrome then an att k may be itiated either by ventr cul t hyarrhythm or by ventricul asystol and either of these mechanisms may in turn be followed by the other (*Fig 1*) Hence during an attack either rapid beating no heart sounds or both may be auscultated and ventricular asystole tachycardia, fibrillation or any combination thereof may be found on the electrocardiogram (ECG) *The findings at particula moment during an attack thus are of littl im th underlying ause is in all*

namely high grade AV block and this is the important fact from the standpoint of treatment

DIFFERENTIAL DIAGNOSIS OF THE STOKES-ADAMS SYNDROME The diagnosis of the Stokes-Adams syndrome is that of the patient with a history of one attack or more often recurrent attacks of unconsciousness of near unconsciousness with or without seizures[13, 43] (Table III) When the Stokes-Adams syndrome has been responsible for the spells, this fact is usually obvious, for even casual ECG s between attacks usually disclose second-degree or high grade AV block—that is, block in the Stokes-Adams syndrome is usually continuous.[9] Occasionally however the block is intermittent and even repeated casual tracings may reveal only normal conduction[4,12 13 43] In such cases, the ECG may still provide evidence of the Stokes-Adams syndrome however by showing QRS contour patterns known to occur in anatomic bilateral bundle branch block[4,1 1 8 22,23,25 40-44] (Table II) The presence of any one of these in a patient with unexplained recurrent unconsciousness, even in the absence of AV block of any kind greatly increases the likelihood that the Stokes-Adams syndrome due to intermittent high-grade block has been responsible for the episodes. Contrariwise, the absence of *both* AV block on several casual ECG s *and* of appreciable QRS widening weighs strongly against the syndrome.

Rarely even an exhaustive clinical investigation including a number of casual ECG s will fail to reveal the underlying disturbance, and in such cases one must resort to continuous monitoring to exclude high-degree AV block. If AV block or another arrhythmia is the cause of the episodes, this approach will if pursued long enough usually provide the diagnosis. Though often tedious and costly this procedure is worth carrying out because of the importance of a correct diagnosis

There is one disorder figuring in the differential diagnosis of the Stokes-Adams syndrome which merits some discussion because it may so closely mimic the latter and because failure to differentiate between the two can lead to therapeutic disaster This condition which we shall refer to as paroxysmal ventricular tachyarrhythmia (PVT) is characterized by paroxysms of ventricular tachycardia or fibrillation due to increased irritability which may produce in a syndrome of episodic syncope clinically indistinguishable from the Stokes-Adams syndrome. *The mechanisms are, however quite different in the latter it is fundamentally the slow ventricular rate which brings about the episodes in the former it is a true increase in ventricular irritability* A report of absent heart sounds or of rapid ones during an attack, or indeed even an ECG showing either ventricular tachyarrhythmia or asystole is of less help in making this distinction than it would first appear for as pointed out above, either asystole or tachyarrhythmia may be observed in the Stokes-Adams syndrome and in PVT since the sudden cessation of a paroxysm of tachycardia may likewise result in prolonged asystole either mechanism may also be observed The most useful differential clues are electrocardiographic and consist of AV block or QRS evidence of bilateral bundle branch block (Table II) or true ventricular irritability as manifest by ectopic activity *in the face of a normal or accelerated rate* In some cases however

Table III Differential diagnosis of recurrent loss of consciousness[12 13]

I Noncardiovascular
- Neurogenic seizures
- Hypoglycemia

II Cardiovascular
- 1 Peripheral
  - Basilar artery insufficiency
  - Vasovagal syncope
  - Orthostatic hypotension
- 2. Cardiac
  - Nonarrhythmic
    - Left ventricular outflow tract obstruction
  - Arrhythmic
    - Sinus node depression
    - SA block[38]
    - Carotid sinus syndrome
    - Primary paroxysmal ventricular tachyarrhythmia ("Irritable ventricle")
    - Advanced or complete AV block (Stokes-Adams syndrome)
      - 1 Continuous
      - 2. Intermittent

the ECG is inconclusive and report must be had to continuous monitoring

The diagnosis of these two conditions is important because the treatment of each is directed oppositely to that of the other In the Stokes-Adams syndrome, the circulatory disturbances are ultimately due to ventricular slowing and the key to management is speeding the heart. If ventricular tachyarrhythmia is a prominent feature, and is misinterpreted as being due to irritability disaster may follow the use of quinidine, procaineamide or a β-blocking agent for these agents will only further slow the rate further increase the degree of block, and further prolong and delay the vulnerable phase. In PVT on the other hand where irritability is the primary underlying cause these drugs are precisely the treatment of choice. Furthermore isoproterenol which is of course absolutely contraindicated in PVT is often beneficial in tachycardia complicating AV block since it usually accelerates the rate and shortens the vulnerable phase more than it enhances ventricular ectopic activity

Finally comment should be made on the problem of episodic syncope in aortic stenosis. Though unconscious attacks in left ventricular outflow tract obstruction usually occur on a hemodynamic rather than on an arrhythmic basis, it should be borne in mind that aortic valve or ring disease particularly calcific aortic stenosis, is not an uncommon cause of bilateral bundle branch block and of Stokes-Adams attacks.[22] Syncope in a patient with aortic valve disease should not, therefore, be ascribed without further thought to hemodynamic causes, nor should the discovery of aortic valve disease in a patient with episodic syncope put an end to consideration of the Stokes-Adams syndrome. Recognition of the syndrome is important in both operable and inoperable cases, for this rhythm disturbance may well prove to be the limiting factor in prognosis, and can be straightforwardly and usually adequately managed with a pacemaker

THE TREATMENT OF THE STOKES-ADAMS SYNDROME. Once the diagnosis of the Stokes-Adams syndrome has been established a pacemaker should be installed. We agree with Dack[23] that this policy should be applied even to patients with mild or infrequent attacks, for the likelihood is that they will have more, any one of which may kill or maim The inability to withstand thoracotomy should no longer contraindicate permanent pacing for the safety and efficacy of permanent intracavitary pacemakers has been thoroughly demonstrated (see below) As pacemakers have become more reliable, the role of drugs in treatment of the Stokes-Adams syndrome has dwindled and though favorable results have been reported in some patients with the long-acting oral sympathomimetic isoprenaline,[24] it is our feeling that drugs have no role in the long term treatment of this condition for none is reliable enough [8,23,4]

As soon as the decision to implant a permanent pacemaker has been made a temporary transvenous device should be inserted This must be done immediately of course, in the patient having frequent attacks, but should not be delayed even in the one who is not. There are several reasons, other than prevention of further attacks, for doing this. First the temporary pacemaker may be used for the hemodynamic and electrophysiological studies which should be performed in all patients in order to establish optimal rate (or rate range) for permanent pacing (see below) Second it allows the heart to shrink before permanent implantation, an important objective particularly if the permanent device is to be an intracavitary one, since shrinkage can result in displacement of the tip Finally if an epicardial device is to be implanted it provides heart rate control during induction and surgery an important consideration for patients with high degree AV block tend to develop serious arrhythmias in the operating room

The prognosis of the untreated Stokes-Adams syndrome is not known and probably never will be since pacemaker treatment cannot now ever be justifiably withheld. The mortality rate in the prepacemaker era was unquestionably formidable, however and probably exceeded 50 per cent within a year of the first attack. [7,24] The effect of long term pacing upon the prognosis is also, of course, unknown, but there is no question that a mod[illegible]

properly installed and competently managed[44] will greatly improve not only the mortality rate but also the morbidity of this condition With regard to the latter it must be said that the mortality data cannot communicate the anxiety and misery of the patient subject to unpredictable attacks of unconsciousness and often convulsions, nor can they reveal the effects of repeated attacks on the more subtle of cerebral functions in these usually elderly people Patients with Stokes-Adams syndrome should not be looked upon as having extensively and hopelessly diseased myocardia for in fact many of them have little or no more *myocardial* disease than their contemporaries who have been spared this electrical disturbance[33,34,3] the older the patient, moreover the more likely this generalization is to apply Pacemakers do not always work well and are still occasionally the source of seemingly endless medical and technological problems The management of the permanently paced patient is often trying and discouraging Nevertheless, there can be no justification for not having installed a pacemaker in a patient damaged or dead because of a Stokes-Adams attack

Implanting pacemakers is no task for the occasional heart surgeon, nor is managing the paced patient one for the physician unacquainted with their medical and technological vicissitudes. Perhaps the ideal arrangement is the pacemaker clinic to which[45] the patient can return at intervals and be referred when problems arise

2. *Circulatory problems resulting from a persistently slow ventricular rate*[3,7, 13,15, 5,6, 3-40] In the previous section we were concerned with the syndrome of episodic, paroxysmal circulatory failure occurring *as a complication of a continuously or* intermittently slow heart rate We shall now consider circulatory problems resulting directly from a persistently and relatively fixed ventricular rate. We discuss these syndromes separately only for convenience they often coexist.

In contrast to the Stokes-Adams syndrome in which the clinical pattern is quite uniform and the manifestations always predominantly cerebral chronic, slow rate circulatory insufficiency may take many forms depending on the ventricular rate, the ability of the myocardium to compensate for it by *increasing its* stroke volume the adequacy of the vascular reflexes, the condition of regional vascular beds (particularly those of the brain and kidney) and the amount of parenchymal disease present in the organs. In most cases, stroke volume is sufficient to produce a normal output at rest but at very slow rates if there is severe myocardial disease, even the resting output may be subnormal and chronic salt and water retention[3,46] congestive heart failure, and chronic encephalopathy[13,31,41] may be present. More commonly however symptoms occur with effort for the (idioventricular) rate rarely rises appreciably with effort and stroke volume cannot increase enough to provide an appropriate output. This may be manifest by a generalized fatigability or by local symptoms such as dyspnea or giddiness. Postural hypotension is also common and is due probably to a combination of poor peripheral vascular reflexes (due to age) to limited output and to the fact that increase in output with rising must depend on stroke volume changes, which are sluggish as compared with those resulting from rate increases. It is notable that angina is rarely a feature of this syndrome most likely because the work of the heart is so limited and diastole so prolonged

The possible etiological relationship between a slow rate and its clinical manifestations suggests itself more readily in some cases than in others. When, for example chronic heart failure exertional dyspnea or postural or effort giddiness occur in a patient with a slow and relatively fixed ventricular rate the symptoms are so obviously cardiovascular in origin that the *possible etiological role of the rate* is usually promptly considered Chronic encephalopathy on the other hand or renal insufficiency are apt to be ascribed to (the usually) advanced age of the patient or to local vascular or parenchymal disease and the role of the bradycardia underestimated or ignored entirely The latter syndromes, particularly encephalopathy are moreover less obtrusive clinical entities in the first place and their very presence may be overlooked[1]

Now that means are available for correcting a slow ventricular rate and for assessing its role in a given case it is our feeling that when a patient with a persistently slow ventricular rate shows any of the above symptoms, the burden of proof should be upon the physician to demonstrate that the bradycardia is *not* playing a significant role, and that all such patients should be considered initially as candidates for permanent pacing. We suggest the following approach. First, measurable parameters appropriate to the case should be selected—electroencephalography or mental testing for example in chronic encephalopathy[44] and representative control data collected over several days. A temporary pacemaker should then be inserted and set at a rate of between 65 and 75 preferably determined from rate output curves (see below). After several days of continuous pacing at this rate (during which tolerance to pacing may be assessed) when a new over all circulatory steady state has had time to develop the measurements should be repeated again over a few days. If in this way a significant improvement can be demonstrated a permanent pacemaker should be installed.[4] One should be cautious in interpreting subjective responses, but they should not be ignored for they will often reveal problems not clinically suspected and constitute real data however difficult they may be to assess.

THE ASYMPTOMATIC PATIENT WITH A PERSISTENTLY SLOW VENTRICULAR RATE. As an extension of the foregoing discussion we should at this point consider the patient with a persistently slow ventricular rate who is apparently well—that is, he does not become short of breath or woozy or unaccountably fatigued in the course of a day's activity, denies postural or effort giddiness, seems normal mentally and shows no clinical or laboratory evidence of heart or kidney failure. Strictly speaking such a patient is asymptomatic, but closer scrutiny will often disclose that his activities, particularly those requiring physical effort are in truth rather curtailed.[44] Such a patient is apt to attribute his limitations to old age and his physician is likely to agree with him, assuming that underlying heart disease or "generalized arteriosclerosis" rather than the slow rate is the limiting factor. While this may indeed be so the probability in a case of this kind is that the bradycardia is contributing to the patient's difficulties.

SLOW RATE PROBLEMS ASSOCIATED WITH DIGITALIS. Patients are occasionally seen in whom digitalis is indicated because of heart failure but in whom the drug so slows the ventricular rate as to preclude its use in—inotropically adequate amounts. This problem is frequent enough to merit separate consideration.

It most commonly arises in patients with atrial fibrillation and a slow ventricular response before treatment; very small quantities of digitalis depress AV conduction to the point that AV dissociation takes place. Since the subsidiary pacemaker in this situation is AV nodal Stokes-Adams attacks are rare (see above) but the ventricular rate is usually reduced to below 60 and held there. The resultant bradycardia may then lead to chronic slow rate circulatory insufficiency as discussed above and may favor the emergence of digitalis-induced ventricular ectopic foci which would be suppressed by faster rates. Similar reductions in the ventricular rate with similar consequences, may also result from sinoatrial block,[29] of which digitalis is the most common cause, and from severe sinus node depression usually in a patient with a pathological sinus bradycardia before treatment.

More often than not these problems can be circumvented for means other than digitalis can adequately control the failure. But some cases resist all such measures, and in these a trial of full digitalization would be most desirable. Temporary pacing can make such a trial possible and should be used without hesitation. If the improvement is substantial a permanent pacemaker preferably of the demand type (since the likelihood of AV conduction is high) should be installed.

3 Recurrent tachyarrhythmia[11,44-46] An important indication for artificial pacing is otherwise refractory recurrent paroxysmal ventricular tachycardia or fibrillation. The use of pacing for this purpose has been discussed in connection with the Stokes-Adams syndrome, probably the most common circumstance in which it is called

The application of suppressive pacing is not limited, however, to the special case in which AV conduction is depressed and the ventricular rate greatly slowed, but extends also to those in which conduction is intact and the heart rate normal or even slightly accelerated.

Tachyarrhythmia is initiated by a ventricular premature beat, usually when it falls into the vulnerable phase of the preceding beat. The key, therefore, to preventing it is to suppress ventricular premature beats. Ectopic foci, regardless of their site, tend to become active or to "emerge" at slow rates and to be dormant or suppressed at faster ones. Thus, the observations that ventricular ectopic activity is especially common in complete AV block and that ventricular premature beats tend to appear at rest (when the rate is slow) and to disappear with exercise (when the rate increases). Pacing may suppress ventricular premature beats by increasing the ventricular rate to one faster than that spontaneous one at which they are occurring and it is in this way that it can be used to prevent tachyarrhythmia.

The trouble, expense, and, more important, the inherent riskiness of pacing are such that it would rarely be the treatment of choice. In most cases, the most notable exception being high-grade AV block, drugs should be tried first. *Atropine* is an agent which has, in this connection, perhaps been neglected. In comparison with other drugs which might be used, and with pacing, it is quite free of serious adverse effects. Since it is sometimes capable of increasing the heart rate to as high a level as is tolerable, it may serve as well as pacing and be useful in predicting the effect of the latter. The drug is certainly worth a trial in patients whose rate is slow or normal. The *β-adrenergic blocking agents* are a group of drugs which will unquestionably find great usefulness in the management of recurrent paroxysmal tachyarrhythmia, though their role is yet to be precisely defined.[71] These agents are, however, associated with side effects which may contraindicate their use. The principal ones, which are cardiac, are *sinus and AV node depression*, which may lead to a number of problems, not the least of which is further "release" of the ectopic focus under treatment, and depression of ventricular functions, which may lead to heart failure or, in outflow tract obstruction and pulmonary hypertension, to acute low output. The former absolutely precludes the use of these agents in AV block and sinus bradycardia, and may necessitate the concomitant use of atropine; the latter absolutely contraindicates their use in severe heart failure and may make digitalization necessary in lesser degrees of decompensation. These agents may also produce bronchospasm and are, therefore, to be used with the greatest caution where this problem is present. β Blocking agents appear to be especially useful in tachyarrhythmia due to digitalis,[8,71] though in this circumstance the presence of diuretic-induced potassium depletion should not be overlooked. In some particularly refractory cases these agents may be employed together with pacing.

Last and still important among the drugs useful in this regard are the classic antiarrhythmic agents, *quinidine* and *procainamide*. Since their action and side effects are so well known, we will mention only one point relative to their use. When ventricular premature beats are very closely coupled and the vulnerable phases of the preceding beats are also delayed and prolonged, drugs of this class tend less to suppress the ectopic focus than to delay and prolong the vulnerable phase still further; thus they may actually enhance the tendency to propagated response and to tachyarrhythmia. This is what takes place in cases of irritability paradoxically increased by these agents.[5,71,72] Therefore, when closely coupled ventricular premature beats follow beats whose QT interval is greatly prolonged, so that the former fall into or almost into the T wave of the latter, quinidine and procainamide should not be used.

If after trial—or at least thought—the use of drugs is abandoned, there should be no hesitation in employing a pacemaker if the situation is serious enough. Either the atrium or the ventricle can serve as the pacing site, but the former is by far the better because it is safer and should be employed if conduction is intact, continuous capture achievable, and the in-

duction of atrial arrhythmias unlikely. Atrial pacing is safer because physiological AV block averts parasystole and because it avoids mechanical provocation of ventricular ectopics by the pacemaker itself. Fixed rate rather than synchronous or demand pacing (see below) is, of course, used. The rate should be increased until either suppression occurs or the rate becomes intolerable because of angina, congestive failure, hypotension, or occasionally increasing ectopic activity. As was mentioned in some cases the use of pacing and β-adrenergic blockade in combination may succeed where either alone has failed.

We have addressed ourselves thus far in this section to tachyarrhythmia of the ventricle and have made no mention of the use of pacing in atrial disturbances. This has not been because pacing is less capable of suppressing atrial tachyarrhythmias but because those in the ventricle are more dangerous and more refractory because the ultimate disturbance, fibrillation, is a relatively safe and easily manageable arrhythmia in the atrium and because the other atrial tachyarrhythmias are usually tractable with conservative measures. One occasionally encounters atrial problems which will neither respond to drugs nor progress to persistent and "manageable" fibrillation; in these atrial pacing may be useful. Notable among the latter is repetitive atrial tachycardia.

Depending on the underlying problem, suppressive pacing may be used temporarily or permanently. Since suppressive pacing is fixed rate pacing, often at fast rates, it should be undertaken most circumspectly and only if prolonged trial with temporary pacing discloses that the rhythm under treatment is, indeed, both persistent and well controlled by pacing.

4. *Advanced and complete AV block complicating acute myocardial infarction.*[illegible] Advanced or complete AV block occurs in acute myocardial infarction (other than as a terminal arrhythmia) with a reported frequency of about 5 per cent.[illegible] It is often said that the true incidence is higher than this, because the disturbance may go undetected and that more aggressive monitoring will increase the frequency.[illegible] While it is true that high-degree block may go unnoticed, it is far more often overdiagnosed and the true incidence is probably considerably less than 5 per cent.

Failure to detect high-degree AV block results in some cases from its transiency and benignity, in others from its abrupt onset and rapidly fatal issue, and in still others, in which it promptly leads to ventricular tachycardia or fibrillation, from its being classified as a primarily tachyarrhythmic disturbance. Overdiagnosis occurs when AV dissociation is erroneously attributed to high grade AV block in cases where it is in fact due to the combination of a slow atrial rate and Type I AV block of relatively low grade, often associated with a slight acceleration of the (nodal) subsidiary pacemaker. This phenomenon, which is very much like what takes place in digitalis poisoning, occurs fairly often in inferior infarction, and its misinterpretation has led to an overestimate of the incidence of advanced and complete AV block in infarction at this site[illegible] and to an underestimate of the over-all mortality rate of (true) high-grade AV block complicating acute myocardial infarction.

The circulatory disturbances resulting from high-grade AV block in myocardial infarction are not essentially different than those occurring in chronic block. They are, however, more severe, for the heart which is the site of acute infarction is far less capable of making the stroke volume adjustments necessary with the slow and is far more prone to tachyarrhythmia than the heart which is not so afflicted. These facts, together with the fact that infarction producing high-grade AV block is generally more extensive and severe, account for the very high mortality rate associated with this arrhythmia.

Heart block complicating acute myocardial infarction may be usefully conceived as taking two rather distinct forms, one tending to appear in anterior and other in inferior infarction.[illegible] The contrasting pathological and clinical features of these two forms are outlined in Table IV. We would caution, however, that, though there is strong tendency for block in acute infarction to conform to one or the other of these patterns and for each pattern to be consonant with the location of the infarct

Table IV. Contrasting features of AV block in anterior and diaphragmatic infarction

	References	Anterior	Diaphragmatic
Incidence	14, 25, 3, 74, 5	1-3 per cent of cases of anterior infarction	7-10 per cent of cases of diaphragmatic infarction
Pathology	11, 25, 29, 30, 74, 76, 77	Massive infarction of summit of intraventricular septum. Infarction of both bundle branches (usually total of right, subtotal of left). AV node and His bundle not involved	Usually extensive infarction extending into infero-posterior septum. Edema, congestion, inflammation (but not infarction) of AV node. No involvement of more distal portions of conducting system (rarely infarction of AV node)
Mortality rate	7, 11, 14, 25, 74, 75, 76, 77	75 per cent	About 40 per cent
		(Over-all mortality rate 50 to 70 per cent)	
Susceptible patient		Patient with severe infarction especially involving high septum. Patient with pre-existing intraventricular block, especially complete LBBB	Patient with severe infarction
Electrophysiological features	3, 4, 5, 7, 23, 25, 76, 29, 30, 53, 4, 75, 6		
a. Level of block		Bifurcation or below	High AV node
b. Type of block		Usually advanced or complete, occasionally preceded by or alternating with Mobitz Type II second degree	Mobitz Type I second degree advanced or complete infrequent
Location of subsidiary pacemaker		Below bifurcation	AV node
d. Ventricular rhythm during dissociation		Rate 25-45 tends to irregularity and arrest	Rate usually between 45-50 regular and stable
QRS contour		QRS widening and patterns associated with bilateral bundle branch block, before and after dissociation	QRS widening usually not present
		Contour changes with onset of dissociation	No change of contour with dissociation
Hemodynamic effect		Paroxysmal and continuous circulatory failure	None as a rule
Role of pacing		Should always be used	Is rarely necessary
Course	14, 25, 73, 75, 6	Tends to persist	Nearly always brief and transient
		Usually leaves residual bilateral or right bundle branch block	Rarely leaves residual conduction disturbance of any sort
		Episodic loss of consciousness common	Episodic loss of consciousness rare

overlapping and exceptions do occur and in a given case the over-all electrophysiological features of the block provide a more reliable guide to its pathogenesis and likely course than does the apparent site of infarction alone.[illegible]

HEART BLOCK ASSOCIATED WITH ANTERIOR WALL INFARCTION. AV block of the type usually associated with anterior infarction results from destruction of the conducting system by massive ischemic necrosis of the summit of the intraventricular septum. The AV node and His bundle are nearly always spared but the right bundle is usually totally destroyed and the left subtotally so. The underlying disease thus consists of anatomic bilateral bundle branch block[illegible] due to necrosis and it is this which gives AV block in this setting its distinctive characteristics (Table IV).

One of the most important of these is that high-grade AV block tends to appear in the early hours of the infarct and suddenly without warning in the form of prior second-degree block. Mobitz Type I block rarely if ever appears in this setting and Mobitz Type II second-degree AV block, though virtually pathognomonic of bilateral bundle branch block and of imminent high-grade block when present, occurs infrequently. The tendency to appear precipitously is one of the most treacherous features of this form of AV block.[illegible] The necrotic nature of the conducting system lesion results also in a tendency for the block to persist and to leave residual block of at least the right bundle branch if the patient survives.

Since AV block of this form is due to anatomical bilateral bundle branch block, it shares many of the electrophysiological characteristics of chronic bilateral bundle branch block described earlier. The most important of these is that the subsidiary pacemaker must be located below the bifurcation, for in the event of dissociation the ventricular rate is slow (less than 45 per minute) and unstable, tending to irregularity and arrest. Another consequence of the level of block is that QRS prolongation, even in conducted beats, is the rule and right bundle branch patterns predominate (Tables I and II). Also, and of the utmost importance since the subsidiary pacemaker must be below the bifurcation, its rate tends to be slow (less than 45 per minute) and unstable.

The risk of complete heart block of this form is higher in the patient with pre-existing bundle branch block because lesser degrees of involvement of the conducting system by the infarct may in such cases summate with the pre-existent lesions. Since infarction more frequently and more severely involves the right bundle branch,[illegible] the patient with prior left bundle branch block stands a particularly high risk.

The appearance during acute myocardial infarction of any sign of bilateral bundle branch block should, in practice, be taken as a sign of impending complete heart block. Since Mobitz Type II block is uncommon and Mobitz Type I block rare in this setting, the only commonly encountered premonitory sign of complete heart block is that of QRS widening, and the latter should be viewed with the greatest concern when it appears during myocardial infarction, particularly if associated with the QRS patterns described in Table III. It should be pointed out that this sign can be detected only electrocardiographically and that other modes of monitoring, however aggressive, will miss it. While bilateral bundle branch block is most likely to occur in anterior infarction, signs of its presence should be considered as having the same pathogenetic and prognostic implications whatever the apparent site of the infarction.

It is to some degree possible to identify those patients particularly prone to develop complete heart block during acute anterior infarction. In general, the higher the septal involvement and the more severe the infarct clinically, the more likely is block to appear. Bundle branch block predating the infarction, especially if complete and left-sided, also augments the risk of complete heart block in anterior infarction. Recognition of the premonitory signs of high-grade block and of those patients in whom the risk of it is particularly high is important, for when it appears, it generally does so without warning in the form of prior second-degree block.

The mortality rate of anterior wall infarction complicated by advanced or complete AV block exceeds 75 per

Isolated second-degree block of lesser severity is so uncommon that no estimate can be made of its mortality rate; it is, however, doubtlessly lower than that of high-degree block.

AV BLOCK ASSOCIATED WITH ACUTE DIAPHRAGMATIC INFARCTION. AV block of the form usually associated with diaphragmatic infarction is quite different. Here the block is located high in the AV node and consists pathologically of edema or inflammation due to transient ischemia or infarction of contiguous myocardium rather than of infarction of the conducting tissue itself. Because of its blood supply, the AV node is rarely infarcted[14,25] and the more distal portions of the conducting system are usually spared because infarction of the diaphragmatic wall rarely extends far enough anteriorly and superiorly to involve them.[25] As would be expected in view of the pathogenesis, block of this form is transient in virtually all cases[1, 13, 25, 34] and rarely leaves residual block of any kind.[13]

The most important characteristics of AV block of this form are that its electrophysiological level is high in the AV node and that its behavior is that of a Mobitz Type I block. Because of the latter, the subsidiary pacemaker (should one emerge) is located in the AV node and has the expected properties of a relatively fast rate, often exceeding 50 per minute[1, 23] and stability. Because the block is of the Mobitz I type, truly high grade block does not often occur; when it does, it does so briefly and in the context of Type I AV block which precedes and follows it and usually, for a time, alternates with it. Advanced or complete AV block, when it occurs, thus rarely does so without warning in the form of premonitory irregularities due to Wenckebach conduction.

When AV block appears in acute diaphragmatic infarction, it is often accompanied by sinus bradycardia which may be marked. In the presence of even low grade AV block located above a potential nodal pacemaker, such sinus slowing favors escape of the latter and, in consequence, long periods of complete or nearly complete AV dissociation readily occur in this situation. This has led to the erroneous impression that advanced and complete AV block are quite common in diaphragmatic infarction.

AV dissociation of this kind differs importantly from that occurring in anterior wall infarction, where it is due to high grade block. The principal difference clinically is that the ventricular rhythm is relatively fast and stable, with none of the tendencies to irregularity and arrest shown by truly idioventricular rhythms. Therefore, neither episodic, paroxysmal circulatory failure with disturbances in consciousness nor chronic circulatory insufficiency is likely to occur due to the rate. If the former occurs, it is more likely the result of tachyarrhythmia due to irritability, and if the latter occurs, to myocardial factors having nothing to do with the rate. If AV dissociation in diaphragmatic infarction is to lead to difficulties, they are apt to be the kind produced by irritable ectopic foci which the hemodynamically tolerable rate is failing to suppress.

Block of the kind ordinarily associated with anterior infarction may occur in diaphragmatic infarction. When it does the underlying lesion is usually bilateral bundle branch block and its course and prognosis is expected with this disorder. At autopsy, cases of this kind are usually found to have either extensive septal infarction or multiple infarctions of various sites and ages.[38]

The mortality rate of diaphragmatic infarction complicated by AV block is about 40 per cent,[7, 3, 13, 18, 22, 24] roughly half that of anterior wall infarction similarly complicated. This lower mortality rate is not surprising in view of the differences in pathogenesis and electrophysiological behavior of the two forms. In lesser degrees of block, the mortality rate is far lower and roughly parallels the severity of block.[22]

THE ROLE OF PACING IN AV BLOCK COMPLICATING MYOCARDIAL INFARCTION. In addition to the characteristics of the block, certain other facts concerning mortality rates and the risks of pacing must be taken into account before defining the role of artificial pacing in block complicating acute infarction. The *first* is that inserting a pacemaker during the acute phase of myocardial infarction is much riskier

than in other circumstances, for the acutely infarcted heart is highly prone to ventricular tachyarrhythmia[75, 81-87] evoked mechanically by the device. This is true not only during insertion itself but, in lesser degree after it is in place as well. The likelihood of parasystole setting off a run of ventricular fibrillation is similarly greater than in other circumstances. Pacing during acute myocardial infarction thus carries substantial risks of its own. The *second* concerns the mortality rate of the untreated condition. The mortality rate of diaphragmatic infarction complicated by heart block (40 per cent) is roughly half that of anterior infarction similarly complicated (75 per cent) but, if we assume the over-all mortality rate of infarction at either site to be about 20 per cent, it becomes apparent that heart block approximately *doubles* the mortality rate of diaphragmatic infarction while it *quadruples* that of anterior infarction. The presence of AV block thus worsens the prognosis far more in anterior than in diaphragmatic infarction. This is not surprising in view of the nature of the block in each case. *Third* it should be borne in mind that the mortality rate of myocardial infarction *associated with* AV block is not the same as that *due to* block. The latter figure cannot be estimated but that it is appreciably lower than the former is suggested by the fact that autopsy in patients who have died of infarction complicated by block usually discloses massive infarctions which would of themselves, regardless of any associated rhythm disturbance, be expected to carry a high mortality rate these infarcts are, for example, surprisingly often the site of perforation.[30, 71] Several investigators estimate that the arrhythmia contributes importantly to the death in less than half of such cases.[7, 18, 30, 3] These facts regarding mortality rates, together with the characteristics of the block in the individual case and the risks of pacemaker insertion during acute infarction all must be taken into account in choosing between a pacemaker and possible alternative modes of treatment[79] in estimating what one might reasonably expect to achieve and in evaluating the results of treatment.

In high-grade block of the form usually associated with anterior infarction, several considerations favor insertion of a temporary pacemaker immediately upon the appearance of the conduction disturbance. The first is that the mortality rate in this situation is so very high that, even though the contributory role of block per se is not known, any reasonable measure which may lower it is justifiable. The second is that block of this form is likely to be persistent, is particularly susceptible to grave hemodynamic and arrhythmic complications, and tends to respond poorly to drug therapy. The wisest course in the patient showing electrocardiographic evidence of bilateral bundle branch block, such as QRS widening or Mobitz Type II AV block but not high-grade block, is less clear but probably also is to insert a pacemaker since these signs are harbingers of dangerous block which should it appear will do so without further warning. At the very least, facilities and equipment for immediate pacing should be held ready in such a case. Finally in the patient with pre-existent complete left bundle branch block any evidence of involvement of the right bundle should be taken as a sign of imminent complete heart block, and a temporary pacemaker inserted.

In AV block due to diaphragmatic infarction pacing is infrequently indicated because of the usually fast ventricular rates during dissociation. When it is necessary it is more often for the purpose of suppressing an irritable ventricular focus than for that of correcting problems due strictly to a slow rate. If circulatory failure is present, it is more likely to be due to myocardial factors than to the rhythm disturbance and will therefore probably not respond to pacing. If pacing is contemplated (whatever the indication) it is usually worthwhile first to attempt to increase the rate with atropine[-11, 2, 30] or corticosteroids[79] and then with isoproterenol[22, 30, 31] these agents are successful in raising the rate in a significant number of cases and may alone suffice in tiding the patient over the usually brief period of slowing. If successful they also provide a means of predicting the eff[illegible] pacing. Particularly valuable [illegible] gard is a trial with isop[illegible]

tient with low cardiac output if this drug with its additional inotropic action increases the ventricular rate without remedying the hemodynamic problem the likelihood of a pacemaker being useful is nil and the risk of inserting one not warranted

The indications for using a pacemaker in AV block of the form seen typically in diaphragmatic infarction would appear therefore to be (1) ventricular irritable foci (2) circulatory failure associated with a rate less than 55 in which drugs have failed to increase the rate or cannot be used because of their side effects and (3) circulatory failure which has responded to isoproterenol but in which this drug can no longer be used because of its toxicity

If heart block subsides, it ordinarily does not recur unless the ischemic process does, [1] [1] but the chances that it may are great enough[1] [11] to warrant leaving *the pacemaker in place for at least two* weeks, so long as it is not itself a cause of difficulty This practice is of course mandatory in cases continuing to show signs of Mobitz Type II or bilateral bundle branch block but probably represents the wisest course in all patients in whom a pacemaker has been required

It will probably never be possible to estimate the effect of pacing upon the mortality rate of acute myocardial infarction complicated by advanced or complete heart block for the mortality rate of the untreated condition is unknown and controlled studies are no longer ethically possible. Comparison even of gross incidence figures obtained now in the era of continuous monitoring with those of previous years will not be valid as more transient milder cases of block are detected the apparent incidence of heart block in the infarction will rise and its mortality rate fall for reasons totally unrelated to pacemaker therapy It is, nevertheless quite certain that the use of pacemakers will reduce the mortality rate.[7 7] Finally it should be pointed out that a small reduction in the over-all mortality rate would constitute a sizable lowering of the mortality rate which block *adds to* that of myocardial infarction alone, particularly in the case of block in anterior *infarction.*

REFERENCES

1 Katz, L. N and Pick, A. The rhythms. Clinical electrocardiography Philadelphia, 1956, Lea & Febiger Publishers.

2 Gilchrist, A. R. Clinical aspects of high-grade heart block, Scott M J 3:53 1958.

3. Kaufman, J G Wachtel, F W Rothfield, E and Bernstein, A. The association of complet heart block and Adams-Stokes syndrome in two cases of Mobitz type of block (Case reports) Circulation 23:253 1961

4 Donoso, E., Adler L. N and Friedberg C. K.: Unusual forms of second-degree atrioventricular block, including Mobitz Type-II block, associated with the Morgagni-Adams-Stokes syndrome Am Heart J 67 150 1964

5 Langendorf R., and Pick, A.: Personal communication.

6 Parkinson, J P pp, C. and Evans, W The lectrocardiogram of the Stokes-Adams ttack, B it. Heart J 33 71 1941

7 Cosby R. S., Lau F Rhode R., Cafferky E., and Mayo, M Complete heart block. Prognostic value of electrocardiographic features nd clinical complications, Am. J Cardiol. 17 190, 1966.

8. Yuceoglu Y Z. L nger M and Dreadale D T Transvenous electrical pacing of the heart. Results of 96 insertions in 78 patients, Am. Heart J 71:5 1966.

9 Zoob, M and Smith K. S. The etiology of complete heart block, Brit. M. J 2:1149 1963.

10 Friedberg, C. K., Donoso, E. and Stein W G Nonsurgical acquired heart block, Ann. New York Acad. Sc. 111:835 1964

11 Harris, A., Bluestone R., and Busby E. The management of heart block, Brit. Heart J 27:469 1965

12. Landegren, J and Biörck, G.: The clinical assessment and treatment of complete heart block nd Adams-Stokes attacks, Medicine 42 171 1963

13 Johansson, B. W Adams-Stokes syndrome. A review and follow up study of 42 cases, Am J Cardiol. 8 76 1961

14. Johansson, B. W : Complete heart block, Acta med. scand nav 180:451 1966.

15 Dack, S. Pacemaker therapy in heart block and Stokes-Adams yndrome J.A.M.A. 191:816, 1965

16. Kantrowitz, A.: Impla table cardiac pacemakers, Ann. New York Acad. Sc. 111 1049 1964

17 Rowe, J C., and White, P D : Complete heart block A follow-up study A n. I t. Med 19:260, 1958.

18. Penton, G B Miller H and Levine, S. A. Some clinical features of complete heart block, Circulation 13:801 1956.

19 Sch edel, J B., and Escher D J W : Transvenous lectrical stim lation of the heart An New York Acad. Sc. 111:972, 981 1964

20. Mueller O F nd Finkelstein, D Adam Stokes syndrome due t Inotrial block, Am. J Cardiol. 17:433 1966.

21 Lev M : The pathology of complete atrio-

ventricular block, Progr Cardiovas. Dis. 6:317 1964.
22 Blondeau, M., and Lenegre J Bloc de branche t bloc uriculo-ventriculaire complet, Arch. Mal. Coeur 57 1 1964.
23 Lenegre, J Etiology nd pathology of bilateral bundle branch block in relation to complete heart block, Progr Cardiovas. Dis. 6:409 1964
24 Lev M The normal anatomy of the conduction system in man and its pathology in trioventricular block, Ann. New York Acad. Sc. 111:817 1964.
25. Blondeau, M., Rizzon, P and Lenegre, J Les troubles de la conduction auriculo-ventriculaire dans l'infarctus m ocardique recent, Arch. Mal. Coeur 54:1092, 1961
26. Langendorf, R. Pick, A and Sorawicz, B. Cause and mechanism of entricular asy tole in advanced A V block, Sorawicz, B and Pellegrino, E. D editors Sudden cardiac death, New York, 1964, Grune & Stratton.
27 Mahaim, I. Les maladies organiques du faisceau de His-T ara, Paris, 1931 Masson & Cie.
28. Y ter W M Cornell, V H., and Clayton, T Auriculo-ventricular block due t bilateral bundle branch lesions A review of the literature and report of three cases with detailed histopathologic studies, Arch Int. Med 57:132, 1936.
29 Lenegre, J Bilateral bundle branch block, Cardiologia 48:134 1966
30 Lev M Unger P N Lesser M E., and Pick, A. Pathology of the conduction system in acquired heart disease Complete right bundle branch block, Am. Heart J 61:593 1961
31 Rosenbaum, M B and Alvarez, A. J The electrocardiogram in chronic chagasic myocarditis, Am. Heart J 50:492, 1955.
32 Porter G. H Sarcoid heart disease, New England J Med. 263:1350, 1960.
33. James, T N Rupe, C. E and Monto, R. W Pathology of the cardiac conduction system in systemic lupus erythematosus Ann. I t. Med. 63:402, 1965
34 Gowans, J D C Complet heart block with Stokes-Adams syndrome due t rheumatoid heart disease Report of case th autopsy findings, New England J Med 262:1012, 1960.
35. James, T N Pathology of the cardiac conduction sy tem in hemochromatosis, New England J Med 271:92, 1964.
36 James, T N and Reynolds E W Pathology of the cardiac conduction system in case of diphtheria associa ed with trial arrhythmias and heart block, Circulation 28:263 1963
37 Nakamura, F F and Nadas, A S. Complet heart block in infants and children, New England J Med 270 1261 1964.
38 Molthan, M E., Miller R., Lobs, A., Hastreiter R., and Paul, M H Congenital heart block with f tal Adams-Stokes attacks in hildhood, Pediatrics 30:32, 196_
39 Campbell, M and Thorne M. N Congenital complet heart block—an acc un f 8 cases, Brit. Heart J 18:90, 1956.
40 Gadboys, H 1 and Litwak, R. S Experimental and clinical aspects of surgical heart block, Progr Cardiovas. Dis. 6:566, 1964.
41 Gannon, P G., Sellers, R. D Kanjuh, V I Edwards, J E., and Lillehei, C. W Complete heart block following replacement of the aortic valve, Circulation 1 (Suppl.) 152, 1966.
42. McGoon, D C., Ongley P A., and Kirklin, J W Surgical heart block, Am. J Med. 37 749 1964.
43 Burchell, H. B., Connolly D C., and Ellis, F H. Indications for and results of implanting cardiac pacemakers Am. J Med. 37 764, 1964.
44. Dressler W Observation in patients with implanted pacemakers. III. Frequency of ventricular tachycardia as cause of Adams-Stokes attacks and rate of pacing required for ts prevention, Am. Heart J 68:19 1964
45 Hoffman, B F and Cranefield, P F The physiological basis of cardiac arrhythmias, Am. J Med 37:670, 1964.
46. Lange, G Action of driving stimuli from in trinsic and extrinsic sources on in situ cardiac pacemaker tissues, Circulation Res. 1 :449 1965.
47 Edelist, A Langendorf, R Pick, A., and Katz, L. N Physiologic and pharmacologic studies in Stokes-Adams disease patients during the use of an artificial cardiac pacemaker I. Effect of rapid artificial timulation on the inherent rate of spontaneous cardiac pacemakers (P) Circulation 28 715 1963
48. Hoffman, B. F and Cranefield, P F Electrophysiology of the heart, New York, 1960 McGraw-Hill.
49 Sokoloff L. Cardiac involvement in rheumatoid arthritis and allied disorders. Current concepts, Mod. Conc Cardiovas. Dis. 33:847 1964
50. Lopez, J F Electrocardiographic findings in patients th advanced and complete AV block. Personal communication.
51 Lasser R. P Haft, J I and Friedberg C. K Relationship of marked left axis deviation and right bundle branch block to heart block, Circulation 34:111-15., 1966 (abstr)
52. Unger P N Lesser M E Kugel, V H., and Lev M The concepts of masquerading bundle branch block An electrocardiographic pathologic correlation, Circulation 1 :397 1958.
53 Lepe-chkin, E. The electrocardiographic diag nosis at bilateral bundle branch block in relation to heart block, Progr Cardiovas. Dis. 6:445 1964.
54. Bluestone, R., and Harris, A Treatment of heart block with long-acting isoprenaline, Lancet 1 1299 1965
55 Bluestone, R., Harris, A and Davies, G Aftercare of artificially paced patients, Brit. M J 1:150 1589 1965
56. Saltzman, P Linn, H and Pick, A. Right bundle branch block with left axis deviation Brit. Heart J 28 703, 1966.
57 Furman, S Escher D J W Sch edel, J B and Solomon, N Trans-venous pacing A seven year review Am Hear J 71:408, 1966.
58 Mueller O F and Bellet, S. Tre tment of intractable heart failure in the presence of complete AV block by the use of he internal cardiac pacemaker—Report of 2 cases, New England J Med. 165:768, 1961

59. Stack, M. F., Rader, B., Sobol, B. J., Farber, S. J., and Eichna, L. W.: Cardiovascular hemodynamic functions in complete heart block and the effect of isopropylnorepinephrine, Circulation 17:526, 1958.
60. Fredberg, C. K., Donoso, E., Stein, W. G., Kahn, M., and Litwak, R.: The role of bradycardia in the retention of sodium and water in complete heart block with and without heart failure in human beings, Am. Heart J. 69:293, 1965.
61. Dalessio, D. J., Benchimol, A., and Dimond, E. G.: Chronic encephalopathy related to heart block. Its correction by permanent cardiac pacemaker, Neurology 15:499, 1965.
62. Segel, N., Hudson, W. A., Harris, D., and Bishop, J. M.: The circulatory effects of electrically induced changes in ventricular rate at rest and during exercise in complete heart block, J. Clin. Invest. 43:1541, 1964.
63. Astrand, I., and Landegren, J.: The effect of varying pacemaker rate on physical work capacity in patients with complete heart block, Acta med. scandinav. 177:657, 1965.
64. Sowton, E.: The relationship between maximal oxygen uptake and heart rate, Brit. Heart J. 27:918, 1965.
65. Sowton, E.: Haemodynamic studies in patients with artificial pacemakers, Brit. Heart J. 26:737, 1964.
66. Herman, D. F., and Helwig, J.: Suppression of ventricular arrhythmias by transvenous pacing, J.A.M.A. 193:1150, 1966.
Sowton, E., Leatham, A., and Carson, P.: The suppression of arrhythmias by artificial pacing, Lancet 2:1098, 1964.
Sowton, E.: Artificial pacemaking and sinus rhythm, Brit. Heart J. 27:311, 1965.
69. Lewis, D. O.: Side effects of propranolol, Brit. M. J. 2:588, 1966.
70. Braunwald, E. (guest editor): Symposium on beta adrenergic receptor blockade (papers on arrhythmias), Am. J. Cardiol. 18:399, 1966.
71. Wolfson, S., Robbins, S. L., and Krasnow, N.: Treatment of cardiac arrhythmias with beta-adrenergic blocking agents. Clinical and experimental studies, Am. Heart J. 72:177, 1966.
72. Binder, M. J., and Rosove, L.: Paroxysmal ventricular tachycardia and fibrillation due to Quinidine, Am. J. Med. 12:491, 1952.
73. Smirk, F. H., and Palmer, D. G.: A myocardial syndrome with particular reference to the occurrence of sudden death and of premature systoles interrupting antecedent T waves, Am. J. Cardiol. 6:620, 1960.
74. Bruce, R. A., Blackmon, J. R., Cobb, L. A., and Dodge, H. T.: Treatment of asystole or heart block during acute myocardial infarction with electrode catheter pacing, Am. Heart J. 69:460, 1965.
75. Courter, S. R., Moffitt, J., and Fowler, N. O.: Advanced atrioventricular block in acute myocardial infarction, Circulation 27:1034, 1963.
76. Julian, D. G., Valentine, P. A., and Miller, G. G.: Disturbances of rate, rhythm and conduction in acute myocardial infarction. A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring, Am. J. Med. 37:915, 1964.
77. Cohen, D. B., Doctor, L., and Pick, A.: The significance of atrioventricular block complicating acute myocardial infarction, Am. Heart J. 55:215, 1958.
78. Hurst, J. W., and Paulk, E. A.: Complete heart block in acute myocardial infarction. A clinical evaluation of the intracardiac bipolar catheter pacemaker, Am. J. Cardiol. 17:695, 1966.
79. Spann, J. F., Moellering, R. C., Haber, E., and Wheeler, E. O.: Arrhythmias in acute myocardial infarction. A study utilizing an electrocardiographic monitor for automatic detection and recording of arrhythmias, New England J. Med. 271:427, 1964.
80. Meltzer, L. E., and Kitchell, J. B.: The incidence of arrhythmias associated with acute myocardial infarction, Progr. Cardiovas. Dis. 9:50, 1966.
81. Katz, L. N.: Effects of artificially induced paired and coupled beats, B. B. New York Acad. Med. 41:428, 1965.
82. Frommer, P. L.: Studies on coupled pacing technique and some comments on paired electrical stimulation, Bull. New York Acad. Med. 41:670, 1965.
83. Singer, D. H., Galst, G., and Wagner, M. L.: Effects of sustained paired stimulation of the heart in normal dogs and in dogs following coronary artery ligation, Bull. New York Acad. Med. 41:652, 1965.
84. Garcia, R., and Keyes, J. W.: Recurrent ventricular tachycardia associated with complete heart block. Observations in a patient with the simultaneous use of a single-stimulus implanted myocardial pacemaker and a coupled-pulse generator, Am. Heart J. 71:533, 1966.
85. Tavel, M. E., and Fisch, C.: Repetitive ventricular arrhythmia resulting from artificial internal pacemaker, Circulation 30:493, 1964.
86. Jensen, O., Allen, H. J., and Mordecai, L. R.: Neomycin contact dermatitis superimposed on otitis externa, J.A.M.A. 197:131, 1966.
87. Parsonnet, V., Zucker, I. R., Gilbert, L., and Meyers, G. H.: A review of intracardiac pacing with specific reference to the use of a dipolar electrode, Progr. Cardiovas. Dis. 6:472, 1964.
88. Thomas, M., and Woodgate, D.: Effect of atropine on bradycardia and hypotension in acute myocardial infarction, Brit. Heart J. 28:409, 1966.
89. Doll, J. L. C.: The effect of steroid therapy on normal and abnormal atrio-ventricular conduction, Brit. Heart J. 26:537, 1964.
90. Krasnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B., and Gorlin, R.: Isoproterenol and cardiovascular performance, Am. J. Med. 37:514, 1964.
91. Zoll, P. M., Linenthal, A. J., Gibson, W., Paul, M. H., and Norman, L. R.: Intravenous drug therapy of Stokes-Adams disease. Effects of sympathomimetic amines on ventricular rhythmicity and atrioventricular conduction, Circulation 17:325, 1958.
92. Harris, A. M.: Endocardial pacing, Am. Heart J. 72:135, 1966.

Fundamentals of clinical cardiology

The syndrome of papillary muscle dysfunction

G. E. Burch, M.D.
N. P. DePasquale, M.D.
J. H. Phillips, M.D.
New Orleans, La.

Normal mitral valve function depends upon the anatomic and mechanical integrity of the atrioventricular ring, the valve leaflets, the chordae tendineae, and the papillary muscles, as well as upon proper integration of the time relations between contraction of the papillary muscle and contraction of the free left ventricular wall. Incompetence of the mitral valve due to congenital or acquired disease of the leaflets, the valve ring, the chordae tendineae, and related structures has long been recognized, whereas incompetence due to disease of the papillary muscles has received relatively little attention. Only recently have advances in the knowledge of papillary muscle function been sufficient to provide a more complete understanding of the over-all physiology and pathology of the mitral valve apparatus. As is frequently the case, through the study of disease the processes of normal function become more evident. This has been so in the areas under consideration, and the manifestations of dysfunction of the papillary muscles have been discussed in previous reports from this laboratory.[1-4] In these reports, emphasis was placed upon the role of ischemia with or without infarction in the development of papillary muscle dysfunction. Although circulatory insufficiency is a major cause of the papillary muscle syndrome, there are many other pathophysiologic states which may result in papillary muscle dysfunction. The purpose of the present paper is to extend concepts previously presented as well as to provide a more comprehensive description of the papillary muscle syndrome. Although only dysfunction of the papillary muscles of the left ventricle is considered in this report, the same concepts may be extended to the papillary muscles of the right ventricle.

Functional anatomy of the normal papillary muscle. Normal papillary muscle function has been described in detail elsewhere[1] and therefore will be discussed only briefly here. There are two groups of papillary muscles in the left ventricle, the anterolateral group and the posteromedial group. The *anterolateral* papillary muscle arises from the anterolateral wall of the left ventricle and receives its blood supply primarily from marginal tributaries of the circumflex branch of the left coronary artery (Fig. 1,A). In some hearts, the anterolateral papillary muscle receives a secondary blood supply from the anterior descending branch of the left coronary

From the Department of Medicine of the Tulane University School of Medicine, the Charity Hospital of Louisiana, and the Veterans Administration Hospital, New Orleans, La.
Supported by grants from the United States Public Health Service, the Rudolph Matas Memorial Fund for the Kate Prewitt Hess Laboratory, and the Rowell A. Billups Fund for Research in Heart Disease.

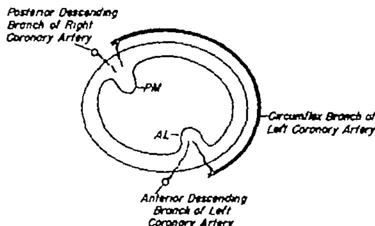


Fig. 1A. Schematic representation of blood supply to the papillary muscles of the left ventricle.

artery (Fig. 1A). The *posteromedial* papillary muscle arises near the junction of the posterior wall of the left ventricle and the interventricular septum and is supplied with blood either by tributaries from the circumflex artery or by posterior descending branches from the right coronary artery (Fig. 1A). Details of the distribution of arterial vessels in the papillary muscles are shown in Figs. 1B and 1C. These small papillary arteries course longitudinally to the apex of the papillary muscle where they terminate in the arterioles, capillaries, venules, and small veins. At times these papillary arteries form arcuate anastomoses near the distal ends of the muscle.

In the normal-sized heart, the long axis of the papillary muscle is oriented almost perpendicular to the atrioventricular ring. This orientation of the papillary muscles provides a mechanical advantage in that tension developed by the papillary muscles is applied almost perpendicular to the mitral valve leaflets. On the other hand, with ventricular dilatation the papillary muscles migrate laterally so that tension developed by the papillary muscles is applied tangentially to the mitral leaflets. The greater the lateral displacement of the papillary muscles the greater the mechanical disadvantage.

The function of the papillary muscles and chordae tendineae to restrain the movements of the mitral valve leaflets during ventricular systole is obvious. However, the dynamic nature of this function is not always appreciated. Normal mitral valve function depends upon the maintenance of the proper spatial relationships between the papillary muscles, the chordae tendineae, and the mitral valve leaflets throughout all phases of the cardiac cycle. During the isovolumetric phase of ventricular systole the rapid rise in intraventricular pressure causes the mitral valve leaflets to bulge towards the left atrium and to come into firm surface contact with each other, thus closing the atrioventricular orifice.[1-4] The movement of the mitral valve leaflets towards the atrium pulls the chordae tendineae taut (Fig. 2). In the interest of completeness it may be stated that there is evidence that the mitral valve leaflets come into apposition to close the atrioventricular orifice just before the onset of ventricular systole.[5] Nevertheless firm apposition of the leaflets probably does not occur until the onset of isovolumetric contraction, at which time the two opposing forces of intraventricular pressure and papillary muscle tension assure that the portions of the mitral leaflets which are in apposition are tightly sealed. It should be understood that the chordae tendineae from each papillary muscle attach to the corresponding halves of *both* leaflets of the mitral valve. However, for purposes of *simplification in illustrating* the hemodynamic consequences of papillary muscle dysfunction, each papillary muscle is shown as supplying a single leaflet in Figs. 1 through 6.

The papillary muscles and chordae tendineae must support the force exerting



Fig. 1B. A longitudinal section through the ventricles of a human heart. The arterial vessels have been injected and filled with finely divided barium sulfate (Micropaque) suspension in 10 per cent formalin. The whitish globules represent areas of extravasation of the barium. *LVC*, Left ventricular cavity; *RVC*, Right ventricular cavity; *IVS*, Interventricular septum; *LVFW*, Left ventricular free wall; *PM*, Papillary muscle; *MVL*, Mitral valve leaflets; *Ba*, extravasated barium. The area enclosed by the rectangle represents that portion illustrated in Fig. 1C.

upon the mitral valve which is equal to the intraventricular pressure times the cross-sectional area of the atrioventricular orifice. In a previous report from this laboratory we have estimated on the basis of certain theoretic considerations, that each papillary muscle of the left ventricle supports a total peak load of 19 tons during a 24 hour period for a heart rate of 70 beats per minute and an arterial blood pressure of 120/80 mm. Hg.

During the ejection phase of ventricular systole the apex of the left ventricle moves towards the atrioventricular orifice. Since the moment-to-moment length of the chordae tendineae is fixed, the papillary muscles must shorten during systole to maintain the proper distance between the base of the papillary muscles and the atrioventricular orifice in order to prevent eversion of a portion of the mitral leaflets into the left atrium. It is of interest that motion pictures of mitral valve movement in the intact dog have demonstrated that the mitral valve leaflets move downward into the ventricle during ventricular systole rather than upward toward the atrium.[11] Thus, contraction of the papillary muscles takes up the slack which would have been created in the chordae tendineae as a result of the shortening of the distance between the apex of the left ventricle and the atrioventricular orifice during the ejection phase of ventricular systole. Furthermore the papillary muscles must develop sufficient tension to overcome intraventricular pressure. This latter point is important since the tension in the free wall of the left ventricle decreases or remains constant during the ejection phase of systole.[12] Therefore while the muscle of the free wall of the left ventricle "loafs" during ventricular ejection the papillary muscles must continue to develop more tension.

Pathologic physiology

Significant alteration in the normal spatial relationships between the papillary muscles, chordae tendineae, and atrioventricular orifice at any time during ventricular systole may result in abnormal function of the mitral leaflets manifested by mitral valve incompetence. However, regardless of its etiology, the hemodynamic consequence of papillary muscle dysfunction, i.e., mitral regurgitation, is always due to alteration in the normal spatial relationships between the various elements of the mitral valve apparatus. Abnormally great tension or restraint on the mitral leaflets may pull the leaflets into the ventricle so that the firm apposition between leaflets necessary for closure of the atrioventricular orifice cannot occur. On the other hand, inadequate restraint on the mitral leaflets allows a portion of each leaflet to evert into the atrium, again preventing satisfactory closure of the atrioventricular orifice. As will be discussed later, a number of disease processes may result in too great or too little restraint on the mitral leaflets by the papillary muscles and chordae tendineae. The time course of the mitral insufficiency varies depending upon the nature of the papillary muscle

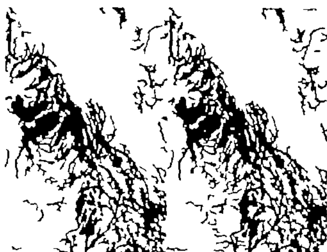


Fig *1C* Stereoscopic presentation of x-ray photographs of barium-filled vessels in the area of the left ventricle demarc ted by the rectangle in Fig *1B* This figure may be viewed stereoscopically by placing a card between the t portions of the illustration and slowly moving the illustration away or toward one s eyes until a three-dimensional relationship is appreciated. With practice nd adjustment of visual distance it is possible t obtain a three-dimensional image of this illustration with the unaided eyes. For those unable to do this stereoscopic lenses ma be employed. In this typical example note the linear distribution of the papillary arteries coursing up through the papillary muscle and also the arcuate anastomosis of some of these vessels near the muscle tip. With such ascular distribution as illustrated here one can readily ppreciate the vulnerability of the distal as of the papillary muscle t ischemic injury

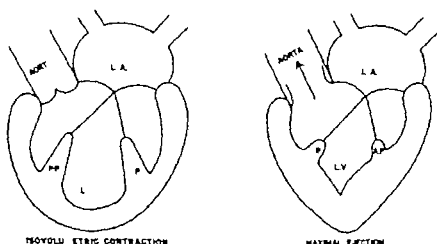


Fig 2. Normal papillary muscle function. For purposes of simplification in this illustration and in Figs. 3 through 6, a single chorda tendinea is depicted as supplying a single mitral leaflet actually hordae tendineae from both papillary muscles supply the correspondin half of each mitral leaflet (consult text). During isovolumetric contraction the mitral leaflets are in ontact nd bulge toward the atrium, pulling the chordae tendineae ta t as intraventricular pressure increases. As the musculature of the ventricle shortens during ejection contraction of the posteromedial (P.P.) and anterolateral (A.P.) papillary muscles maintains a proper distance bet een the papillary muscles and al leaflets thus keeping the mitral valve closed during systole (From Burch DePasquale and Phillips Arch. Int. Med. 112:112, 1963)

dysfunction so that the characteristics of the associated murmur often provides a clue to the etiology of the papillary muscle dysfunction.

Etiology

As already indicated papillary muscle dysfunction may be due to a variety of disease processes (Table I) and regardless of whether the papillary muscle dysfunction is due to loss of anatomic or functional integrity mitral incompetence is always due to alteration in the normal spatial relationships between the papillary muscles, chordae tendineae, and atrioventricular orifice. Diseases involving the chordae tendineae are included among the causes of papillary muscle dysfunction in Table I because the papillary muscles and chordae tendineae function as a unit. However it should be clear that mitral valve disease with or without involvement of the chordae tendineae should not be considered as an example of the papillary muscle syndrome

Table I. Etiology of papillary muscle dysfunction

- Circulatory insufficiency (ischemia)
  - Angina pectoris
  - Infarction of papillary muscle
    - Acute
    - Chronic (fibrosis)
  - Systemic circulatory disturbances (hypotension, erythrocytosis anoxia, hematometakinesia, etc.)
- Left ventricular dilatation
  - Generalized
  - Localized (aneurysm)
- Nonischemic atrophy of papillary muscle
  - Senile
  - Associated with cachexia
- Defective development of papillary muscle apparatus
  - Congenitally long or short papillary muscle or chordae tendineae
  - Ectopic origin of papillary muscle
  - Ectopic insertion of chordae tendineae
- Endocardial disease
  - Endocarditis
  - Endocardial fibroelastosis
  - Endomyocardial fibrosis
- Heart muscle disease
  - Inflammatory (myocarditis)
  - Degenerative cardiomyopathy
  - Infiltrative (metastatic carcinoma, amyloidosis)
  - Neoplastic (primary tumor of myocardium)
- Disturbances in the time course of papillary muscle activation and contraction
- Rupture of papillary muscle or chordae tendineae

Circulatory insufficiency Probably the most common cause of papillary muscle dysfunction is circulatory insufficiency The papillary muscles being subendocardial structures, are supplied by terminal branches of the coronary arteries (Figs. 1*A* 1*B* and 1*C*) Moreover they are the thickest portion of the endocardium. These factors combine to render the papillary muscles particularly vulnerable to ischemia. The papillary muscles may become ischemic not only as a result of narrowing of the coronary arteries but also as a result of disease states associated with diminished coronary artery perfusion. Because of the large amounts of tension which must be developed by the papillary muscles during ventricular systole, they are easily damaged by ischemia. Furthermore, in some hearts the major blood supply to both papillary muscles of the left ventricle is derived from the same artery (circumflex branch of left coronary artery) so that the risk of simultaneous ischemia of both papillary muscles is increased. The great vulnerability of the papillary muscles to ischemic damage is emphasized by the fact that one or both papillary muscles showed evidence of recent or old infarction in 25 per cent of 422 consecutive hearts studied at necropsy [12]

During episodes of ischemia or following infarction of a papillary muscle the muscle is rendered completely or partially incapable of contraction Providing that the heart is not enlarged the normal spatial relationships between the elements of the mitral valve apparatus are maintained during isovolumetric contraction and the valve is competent (Fig 3) However during ventricular ejection the slack created in the chordae tendineae by the apex-to-base movement of the left ventricle is not taken up because of the inability of the ischemic papillary muscle to shorten (Fig 3) Thus, a portion of *each* mitral valve leaflet everts into the left atrium and the valve becomes incompetent. If the ischemia is only transitory as during an episode of angina pectoris, clinical evidence of mitral valve incompetence rapidly subsides as the ischemic papillary muscle regains the ability to contract. On the other hand following infarction of a papillary muscle the clinical

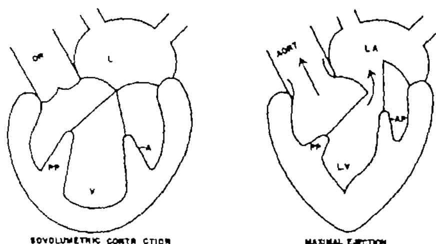


Fig. 3. Papillary muscle dysfunction following infarction or ischemia of the anterolateral papillary muscle. Although the papillary muscle cannot contract (shorten) the mitral valve leaflets remain closed during isovolumetric contraction. However failure of the papillary muscle to shorten during ejection creates a situation in which the portion of each mitral leaflet supplied by chordae tendineae from the noncontracting papillary muscle everts toward the atrium. The murmur in this instance, begins after isovolumetric contraction. Ventricular dilatation may modify the characteristics of the murmur (see Fig. 5) (From Burch DePasquale and Phillips Arch. Int. Med. 112 112, 1963).

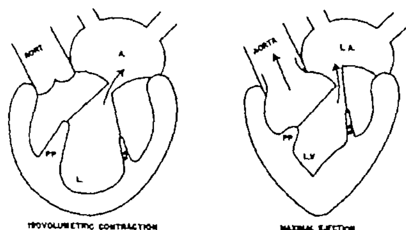


Fig. 4. Fibrosis and atrophy of the anterolateral papillary muscle is depicted as pulling a portion of the mitral leaflet into the ventricle during isovolumetric contraction and allowing a portion of the valve to evert into the atrium during ventricular ejection. The resulting murmur is variable depending upon the degree of fibrosis and the state of the myocardium (From Burch DelPasquale and Phillips Arch. Int. Med. 112 112 1963).

signs of mitral incompetence usually regress slowly as the papillary muscle gradually recovers. The changing characteristics of the murmur associated with papillary muscle dysfunction as a result of infarction of the muscle will be discussed later. It should be pointed out however that the sudden development of an apical systolic murmur after myocardial infarction is much more often due to papillary muscle dysfunction than to rupture of a papillary muscle or perforation of the interventricular septum.

When ischemia and/or infarction results in diffuse scarring degeneration and atrophy of a papillary muscle the retracted muscle pulls a portion of each mitral leaflet into the ventricle so that the valve is incompetent even during isovolumetric contraction (Fig. 4). During

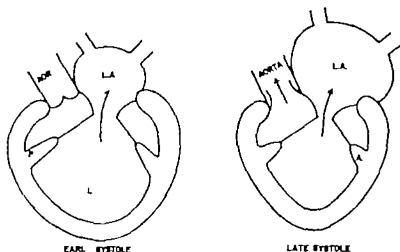


Fig 5 Left entricular dilatation results in centrifugal migration of the papillary muscle y from the trio entricular orifice th retraction of the mitral leaflets into the ventricle I addition, both papillary muscles are t mechanical disadvantage because they must exert tension against intra entricular pressure more tangentially than normally The murmur begins immediately after the first heart sound because the valv is incompetent during iso olumetric contraction. However t may decrease in intensity during entricular ejection because of better approximation of the lv leaflets.

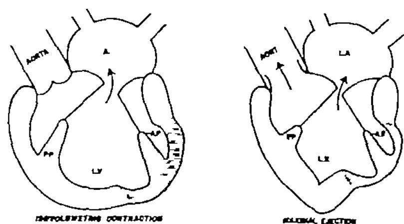


Fig. 6 Papillary muscle dysf nction resulting from the incorporation of the anterolateral papillary muscle int neurysm of the left entricle (consult text) (Arch I t Med. 112 158 1963)

the ejection phase of systole the apex-to-base movement of the left entricle may permit better apposition of the mitral alve leaflets so that the degree of valve incompetence decreases.

Left ventricular dil t tion Left ven tricular dilatation is a frequent cause of papillary n uscle dy function Under such circum tances the papillary muscles ma contr ct normally but the spatial rela t onsh ps between the papillary muscles, the chordae tend neae and the A V orifice are altered by the dow ward and lateral or centrifugal migration of the wall of the left ventricle away from the A V orifice (Fig 5) The valve leaflets are thus pulled downward into the left entricle so that they are incompetent In add tion the axis of the papillary muscles becomes more ol lique with respect to the atrio-ventricular orifice Under uch circumstances the papillary muscles exert ten sion on th mitral valve leaflet more tangentially than normally an obviou me

chanical disadvantage Thus even when ventricular dilatation is associated with compensatory elongation of the chordae tendineae[1] mitral incompetence may occur The blowing apical systolic murmur which is often heard in patients with left ventricular dilatation is frequently considered to be due to dilatation of the annulus of the mitral valve However because (1) the annulus of the mitral valve consists of dense fibrous tissue which is not easily distended (2) the surface area of the mitral valve leaflets is about 2 5 times the area of the atrioventricular orifice[5] and (3) the mitral annulus contracts during systole[13] it would appear unlikely that simple dilatation of the mitral annulus would result in mitral regurgitation In our opinion papillary muscle dysfunction is a much more likely explanation for the apical systolic murmur associated with left ventricular dilatation than is dilatation of the mitral annulus. Since the mitral valve leaflets are pulled downward into the left ventricle in the dilated heart the valve is incompetent during isovolumetric contraction However as the left ventricle contracts, the valve leaflets may be brought into better apposition so that the degree of mitral incompetence decreases as systole progresses (Fig 5) An exception to the above exists when the papillary muscle is incorporated in an aneurysm of the ventricle. Because of paradoxical movement of the aneurysm outwards during ventricular contraction the degree of mitral incompetence increases rather than decreases as systole progresses (Fig 6)

Nonischemic atrophy of papillary muscle Atrophy of a papillary muscle due to ischemic degeneration with fibrosis is a fairly common finding at necropsy In addition it is not uncommon to observe atrophy of one or both papillary muscles of the left ventricle in the absence of ischemia in hearts of older patients or in patients who have died of debilitating disease. We have observed many hearts at autopsy in which an atrophic papillary muscle was no larger than the trabeculae carneae. The atrophic papillary muscle exerts excessive traction on the mitral valve leaflets, pulling them downward into the left ventricle so that the mitral valve is incompetent. Thus, atrophy of one or both papillary muscles must be considered among the causes of mitral incompetence, a fairly frequent finding in older patients.

Defective development of the papillary muscle apparatus We have had little experience with defective development of the papillary muscle apparatus as a cause of the papillary muscle syndrome Nevertheless, it is obvious that congenitally short or long chordae tendineae ectopic insertion of the chordae tendineae, or ectopic origin of a papillary muscle would result in alteration of the normal spatial relationships between the various elements of the mitral valve apparatus and in an incompetent mitral valve.[14-16] However as judged from a personal study of over 3 000 hearts at autopsy during the past ten years at the Veterans Administration Hospital in New Orleans, defective development of the papillary muscle apparatus must be a rare cause of mitral incompetence at least in adult men

Endocardial disease In endocardial sclerosis of the left ventricle mitral incompetence may develop as a result of involvement of the chordae tendineae and papillary muscles in the fibrotic process so that excessive retraction of the mitral leaflets prevents closure of the atrioventricular orifice during systole.[19] It is well known that apical systolic murmurs occur frequently in children with subendocardial fibroelastosis. Levy and Edwards[17] have suggested that the mitral incompetence in children with subendocardial fibroelastosis is due to short papillary muscles and chordae tendineae which exert excessive restraint upon the mitral valve leaflets rendering them incapable of firm apposition. Since subendocardial fibroelastosis is often associated with left ventricular dilatation lateral migration of the papillary muscles must also contribute to the development of mitral incompetence.

Heart muscle disease (cardiomyopathy) There is increasing awareness among clinicians and perhaps even among pathologists that there are a group of diseases which involve the heart muscle without affecting other cardiovascular structures. Such diseases have been categorized as primary myocardial disease heart muscle



Fig. 7. Direct fluorescent antibody stain of a papillary muscle of a mouse inoculated with Coxsackie virus B. The light areas identify the presence of viral antigen throughout the papillary muscle.

disease, or cardiomyopathy.[30,31] Although there is no general agreement on which diseases should be classified as heart muscle disease, some of the diseases presently included in this category may be associated with papillary muscle dysfunction.

As already indicated, the papillary muscles perform a great deal of mechanical and metabolic work. It may be for this reason that they are so vulnerable to inflammatory disease. For example, viral myocarditis, which usually has a patchy focal distribution, often extensively involves the papillary muscles. Fig. 7 shows the papillary muscle of a mouse inoculated with Coxsackie virus B, in which viral antigen demonstrated by direct fluorescent antibody staining can be identified throughout the muscle. Whether or not a portion of the papillary muscle as shown in Fig. 7 is capable of contraction is unknown. However, it is well known that apical systolic murmurs are often audible during episodes of myocarditis and that such murmurs frequently subside after recovery from the myocarditis.[32]

Other primary myocardial diseases such as amyloidosis, sarcoidosis, and glycogen storage disease may result in impaired contraction of a papillary muscle for obvious reasons.

Disturbances in the time course of papillary muscle activation and contraction. In order to maintain the proper spatial relationships between the various elements of the mitral valve apparatus and the papillary muscle system, not only must the papillary muscles be structurally and functionally normal but they must also be activated in proper time sequence relative to activation of the free wall and other parts of the left ventricle. The papillary muscles are richly supplied with Purkinje fibers and are activated before the muscle of the free left ventricular wall.[33,?] Thus, they are already in a state of tension when the intraventricular pressure increases during isovolumetric contraction so that they are prepared to support the force acting upon the mitral valve. There is a critical relationship between papillary muscle activation and activation of the free wall of the left ventricle. Activation of a papillary muscle too early or too late will result in mitral incompetence. For example, asynchronous contraction of a papillary muscle probably contributes to the mitral incompetence observed during premature ventricular contractions or disturbances in intraventricular conduction of the activating impulse. There are many possible variations in the timing during the cardiac cycle and the degree of mitral regurgitation, depending upon the time course of papillary muscle activation. Indeed, alterations in the timing of papillary muscle activation relative to free wall activation may be responsible for at least some of the peculiar apical midsystolic sounds which are difficult to explain at present on the basis of the known hemodynamic facts.

Rupture of papillary muscle or chordae tendineae. Rupture of a papillary muscle or one or more chordae tendineae results in severe mitral regurgitation because of loss of restraint of the mitral leaflets and eversion of the leaflets into the atrium. However, rupture of a papillary muscle or chorda tendinea is a relatively rare event. Papillary muscle rupture usually occurs in the posteromedial papillary muscle as a result of myocardial infarction and necrosis.[35,36] Rupture of a chorda tendinea may occur secondary to bacterial endocarditis, trauma, rheumatic heart disease, or various connective tissue disorders, such as Marfan's syndrome.

Clinical manifestations

As already indicated, the time course of mitral regurgitation in patients with the papillary muscle syndrome depends upon

the nature of the dysfunction In the discussion of clinical manifestations to follow emphasis will be given to papillary muscle dysfunction due to ischemic heart disease However with knowledge of normal mitral valve function and the underlying disease the auscultatory manifestations associated with each type of papillary muscle dysfunction can be readily understood

Symptomatology In general the papillary muscle syndrome is not associated with specific symptoms symptomatology being related more to the disease responsible for the papillary muscle dysfunction than to the dysfunction per se However particularly in patients with ruptured papillary muscle or chordae tendineae symptoms related to left ventricular failure may develop directly as a result of the papillary muscle dysfunction

Since ischemic heart disease is one of the most common causes of papillary muscle dysfunction most patients with the syndrome are past the fourth decade in age Obviously any of the manifestations of ischemic heart disease may accompany the papillary muscle dysfunction including angina pectoris myocardial infarction and congestive heart failure all of which play an important role in the determination of the auscultatory findings.

Physical finding Failure of a papillary muscle to contract during ventricular systole in a patient with a normal or only slightly dilated heart is associated with an apical systolic murmur the characteristics of which are often unlike those of mitral insufficiency of rheumatic origin The murmur of rheumatic mitral regurgitation is typically pansystolic and tends to be of uniform intensity (plateau) with possibly minimal late systolic accentuation[27,28] On the other hand the murmur associated with a "mechanically silent" papillary muscle due to failure of the muscle to contract is often delayed in onset, crescendo-decrescendo in quality (diamond shaped) with midsystolic accentuation (Fig 8) Thus it frequently appears to have the qualities of an "ejection" murmur The murmur is soft to moderately loud in intensity and tends to be somewhat "blowing" in quality It is heard best at the apex radiates to the axilla and is only rarely associated with a thrill The murmur is also occasionally well transmitted to the aortic area, a finding which when evaluated in the light of the ejection qualities of the murmur may cause some difficulties in differential diagnosis. It should be emphasized that failure of a papillary muscle to contract is not invariably associated with the murmur described above. Myocardial infarction is a frequent cause of a noncontracting papillary muscle and this combination of lesions is commonly accompanied by left ventricular dilatation and congestive heart failure. Under these circumstances the mitral valve leaflets are retracted downward into the left ventricle so that the murmur begins with the first heart sound Furthermore as the ventricles contract failure of the papillary muscle to contract may actually compensate for the altered spatial relationships between the elements of the mitral valve apparatus so that the valve leaflets come into better apposition as systole progresses and the murmur has a decrescendo quality A disordered sequence of activation of the



Fig 8 Schematic representation of a type of murmur frequently caused by failure of the papillary muscle to contract in the absence of left ventricular dilatation or other disturbances of the mitral valve system. Because the spatial relationships among the various elements of the mitral valve apparatus are normal during isovolumetric contraction, the valve is competent during this phase of ventricular systole However with the onset of ejection, failure of the papillary muscle to contract results in eversion of a portion of each mitral leaflet into the atrium and mitral insufficiency Note that the murmur is "diamond-shaped" or ejection in quality In this instance the murmur is depicted as ending before the second heart sound. However the murmur may be holosystolic depending upon whether or not left ventricular decompensation and/or left ventricular dilatation are present If the ventricle is significantly dilated the murmur is earlier in onset beginning immediately after the first heart sound

papillary muscles in relation to the other muscles of the left ventricle may also contribute to alterations in the characteristics of the associated murmur.

The constancy of the physical findings in a given patient with a noncontracting papillary muscle depends upon the activity of the underlying disease. The murmur accompanying healed infarction or fibrosis of the papillary muscles tends to be constant even over extended periods of observation. In some patients the murmur has been noted to remain virtually unchanged over periods of two to three years. In contrast, during the course of acute myocardial infarction involving the papillary muscles or during episodes of prolonged but fluctuating coronary insufficiency, the murmur may be present for several hours or days, only to disappear completely as the coronary circulation improves and then to return with exacerbation of the coronary insufficiency. The characteristic auscultatory findings of a noncontracting papillary muscle may be present even during transient episodes of angina pectoris. These findings tend to disappear as the attack subsides spontaneously or through the use of carotid sinus pressure or glyceryl trinitrate. Thus papillary muscle dysfunction due to failure of the muscle to contract and the associated mitral regurgitation may be present as a fixed lesion or may exist as a changing disorder.

With the exception of the auscultatory findings, no other physical findings are consistently associated with the papillary muscle syndrome. As might be expected, signs of cardiac enlargement and gallop rhythm (both ventricular and atrial) are frequently observed but are nonspecific with respect to the syndrome. Moderately wide splitting of the two components of the second heart sound at the pulmonic area, which may possibly be related to the degree of mitral regurgitation, is occasionally noted. To the present time late systolic clicks have not been observed as a feature of the papillary muscle syndrome secondary to acquired ischemic disease.

Differential diagnosis. The murmur of papillary muscle dysfunction due to failure of the muscle to contract properly must be distinguished from the following entities: (1) mitral regurgitation due to rheumatic valvulitis, (2) aortic stenosis, (3) rupture of the papillary muscle or chordae tendineae, (4) the so-called "late systolic murmur," and (5) rupture of the interventricular septum. It should be pointed out that the demonstration of the rather typical electrocardiographic findings of papillary muscle fibrosis or infarction to be described below is of considerable value in differential diagnosis.

Mitral regurgitation due to rheumatic valvulitis may occasionally cause some difficulty in differential diagnosis. A past history of rheumatic fever and a history of onset of the murmur at an early age are of obvious importance in differential diagnosis. As noted above, the murmur of rheumatic mitral insufficiency is characteristically pansystolic and does not have a "diamond-shaped" configuration. It is frequently louder and much more frequently associated with a thrill than the murmur of papillary muscle dysfunction. Helpful ancillary findings in differential diagnosis are the facts that rheumatic mitral insufficiency is associated with a much greater degree of left atrial enlargement as detected electrocardiographically and roentgenographically and is much more likely to be associated with mitral valve calcification than is mitral insufficiency secondary to papillary muscle dysfunction.

It is well established that murmurs of aortic stenosis and mitral insufficiency may masquerade as one another.[29] Because the murmur of papillary muscle dysfunction may have an "ejection" quality and may radiate to the aortic area, confusion with the murmur of aortic stenosis can occur. However, the murmur of aortic stenosis tends to be harsher than that of papillary muscle dysfunction. Furthermore, in aortic stenosis the two components of the second heart sound may be only narrowly split or display paradoxical variation with respiration and the aortic component may be reduced in intensity, whereas in papillary muscle dysfunction the two components of the second heart sound are normally or even widely split and the aortic sound is of normal intensity. In the presence of atrial fibrillation the

murmur of aortic stenosis tends to be more accentuated following a long diastolic pause[28] than is the murmur of mitral insufficiency due to papillary muscle dysfunction The amyl nitrate test[31] may be of value in distinguishing between the murmur of aortic stenosis and that of mitral regurgitation In this test, careful auscultation and/or phonocardiography is carried out while and immediately after the patient inhales amyl nitrate The murmur of papillary muscle dysfunction becomes softer during and approximately 20 seconds after inhalation of amyl nitrate whereas the murmur of aortic stenosis becomes louder reaching a peak intensity approximately 30 to 45 seconds after inhalation Additional clinical data such as onset of the murmur at an early age exertional syncope narrow pulse pressure slow rising pulse of small volume demonstration of calcium in the aortic valve or root and poststenotic dilatation of the aorta favor the diagnosis of aortic stenosis rather than papillary muscle dysfunction.

Rupture of the mitral valve of the chordae tendineae or of a papillary muscle results in a loud apical systolic murmur which is often of ejection type or diamond shaped [illegible] This murmur may radiate to the aortic area where it may be confused with the murmur of aortic stenosis. It is most important to distinguish between the murmur of papillary muscle dysfunction due to rupture of the mitral valve chordae tendineae or papillary muscle and the murmur of papillary muscle dysfunction due to infarction or ischemia of a papillary muscle without loss of continuity among the various elements of the mitral valve apparatus. Under both sets of circumstances the murmur may be loud ejection in type and associated with wide splitting of the second heart sound In addition infarction of a papillary muscle with rupture results in electrocardiographic alterations similar to those of infarction of a papillary muscle without rupture. Thus distinction between mitral insufficiency due to papillary muscle dysfunction with and without loss of continuity among the various elements of the mitral valve apparatus may occasionally be difficult Nevertheless, rupture of either a papillary muscle or the chordae tendineae usually results in rapid deterioration of the clinical state of the patient with congestive heart failure and death often occurring within 24 hours. Such a sudden and dramatic demise does not occur in the papillary muscle syndrome. Although the murmur associated with rupture of a papillary muscle or of chordae tendineae may be diamond-shaped and have a midsystolic accentuation unlike the murmur of papillary muscle dysfunction without loss of continuity it tends to be early in onset may be associated with a thrill [illegible] and is usually very loud and holosystolic.

The so-called late apical systolic murmur has been a source of great interest recently [illegible] These murmurs are mostly confined to the latter part of systole, at which time they assume a crescendo or crescendo–rapid decrescendo configuration. They are frequently but not invariably associated with one or more mid to-late systolic clicks (nonejection type) Their origin was originally thought to be extracardiac, perhaps from old pericarditis[illegible] but more recently it has generally been agreed that most if not all are associated with some degree of mitral insufficiency [illegible] The exact defect involved is not yet well delineated but abnormalities of the papillary muscle chordae tendineae and/or mitral leaflets have been suggested There is good evidence that, in some instances, the defect responsible for the murmur is congenital in origin with familial propagation.[illegible] The occurrence of such a murmur in Marfan's syndrome has been noted.[illegible] The typical murmur has been shown to be temporally related to angiocardiographically demonstrated mitral regurgitation [illegible] It has been suggested that the systolic click frequently associated with the late systolic murmur is due to sudden tensing of slack chordae tendineae ("chordal snap")[illegible] and hence the term nonejection click Angiocardiography in patients with the late apical systolic murmur has not only demonstrated mitral regurgitation but has also displayed abnormal doming or bulging of the posterior (septal) mitral leaflet[illegible] and even aneurysmal protrusion of the leaflet [illegible]

It is of interest that a number of patients with late systolic murmurs have chest pain and electrocardiographic ab

normalities consisting of ST-segment depression and T wave inversion in Leads II, III, aV$_F$, V$_5$, and V$_6$ and peaked tall T waves in the midprecordial leads (V$_2$ to V$_4$).[44,45,46] It is in this group especially that the possibility of ischemic papillary muscle dysfunction as an etiologic factor might be raised. However, Barlow and Bosman[45] have suggested that abnormal mitral valve function is more likely the cause of the murmur than ischemic disease.[46] Although it is yet to be demonstrated, these authors postulated that aneurysmal dilatation of the posterior mitral leaflet distorts the circumflex coronary artery, thereby resulting in the ischemic features of the disorder. Although there are superficial similarities, mitral insufficiency of the type associated with the late systolic murmur should not be confused with the insufficiency due to ischemic papillary muscle dysfunction. For in the latter, the murmur is usually (but not invariably) loudest in midsystole and typically is not associated with systolic clicks.

Because of its occurrence in association with acute myocardial infarction, rupture of the interventricular septum must be considered in the differential diagnosis of papillary muscle dysfunction. Septal rupture is not an extremely rare complication of myocardial infarction.[47-49] Rupture of the interventricular septum usually leads rapidly to congestive heart failure and early death. There is usually both left and right ventricular failure, frequently with evidence of tricuspid insufficiency. The associated systolic murmur may be accompanied by a thrill and is most intense in the fourth left intercostal space close to the sternum. Although the murmur may be "diamond-shaped" in configuration, it is usually holosystolic in timing and duration. If the above characteristics are kept in mind, confusion with papillary muscle dysfunction can usually be avoided. Electrocardiographic differences may be of further aid in differential diagnosis.

Electrocardiography

Although papillary muscle dysfunction may be the result of a number of disease processes, the electrocardiogram (ECG) has been studied in detail only in papillary muscle dysfunction secondary to circulatory insufficiency. Electrocardiographic criteria for the recognition of infarction and/or fibrosis of the papillary muscles have been confirmed at autopsy. The criteria for diagnosis of anterolateral papillary muscle involvement have been presented in detail elsewhere, and preliminary data on the recognition of posteromedial muscle involvement have been mentioned.[3] Since these publications, additional data have been accumulated.

Studies of infarction or fibrosis of the anterolateral papillary muscle have delineated electrocardiographic changes of three basic types with some overlapping between types. *Type I* consists of mod

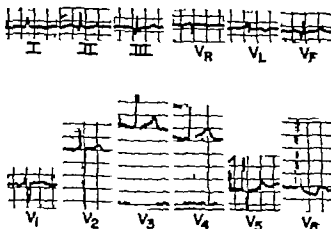


Fig. 9. ECG display ng Type I alterations in ischemic disease of the papillary muscle (consult text).

erate depression of junction J with concavity upward or slight convexity-downward deformity of the ST T interval (Fig 9) Type II consists of slight to moderate depression of junction J but with a prominent convexity upward deformity of the ST T interval and terminal inversion of the T wave (Fig 10) Type III consists of marked depression of junction J usually associated with a slight convexity upward (occasionally concavity upward) deformity of the initial ST T interval (Fig 11) In general the Type I pattern is associated with chronic fibrosis of the papillary muscle Type II with prolonged ischemia of the papillary muscle and Type III with acute circulatory insufficiency or infarction of the papillary muscle It should be emphasized that prolongation of the QT interval and T U segment or U wave abnormalities are extremely common in each of the three electrocardiographic types. In anterolateral papillary muscle involvement the electrocardiographic changes described above occur predominately in Leads I aVL V₅ and V₆ whereas in posteromedial papillary muscle involvement these changes are found predominately in Leads II III aVF and or V₁ through V₄. Because involvement of both papillary muscles is not unusual there may be overlapping of the findings. Fur

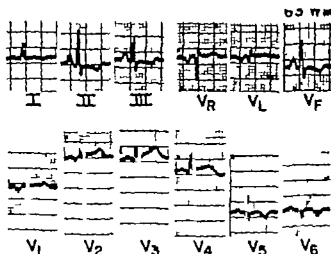


Fig 10 ECG displaying Type II alterations ischemic disease of the papillary muscles (consult text).

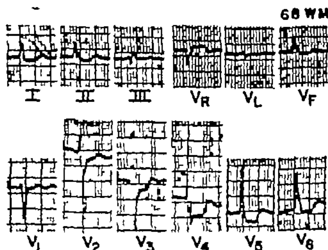


Fig. 11 ECG displaying Type III alterations in ischemic disease of the papillary muscles (consult text).

thermore it should be noted that detailed electrocardiographic studies have been carried out only in ischemic papillary muscle dysfunction and there is a need for such studies in other types of papillary muscle involvement

Although the electrocardiographic changes described above are not pathognomonic of ischemic disease of the papillary muscles, their predictive value, as determined at autopsy has proved to be remarkably accurate. As pointed out before however one or especially a combination of the following could lead to difficulty in interpretation left ventricular hypertrophy the shock syndrome (especially if treated with potent vasopressor agents) subendocardial infarction or hemorrhage not necessarily involving a papillary muscle digitalis and quinidine (or procaine amide) effect post tachycardia syndrome coronary insufficiency severe disturbance of intraventricular condition and electrolyte imbalance. Somewhat surprisingly these factors have rarely proved troublesome except in the presence of extreme left ventricular hypertrophy associated with either severe diastolic hypertension or severe aortic valvular insufficiency In these clinical states the Type I or Type II electrocardiographic pattern of papillary muscle involvement may be simulated Electrocardiographic evidence of severe left ventricular hypertrophy and dilatation is usually superimposed however and is of aid in differential diagnosis.

It should be noted that only a little more than half of the patients with typical electrocardiographic findings of papillary muscle fibrosis or infarction will have the characteristic auscultatory features of the syndrome. Furthermore there is no doubt that the physical findings of papillary muscle dysfunction may occur in the absence of typical electrocardiographic changes, but the frequency of this occurrence has not yet been tabulated.

Other laboratory data

Phonocardiography has confirmed the auscultatory features of papillary muscle dysfunction as outlined above Because a large majority of patients with this disorder have serious ischemic heart disease few hemodynamic studies are available Holloway and associates[29] recently reported data obtained by right and left heart catheterization in two patients with papillary muscle dysfunction Of course of great interest was their confirmation of mitral insufficiency by cinefluorography and indicator dilution studies.

Summary

The function of the papillary muscles to restrain the mitral valves is obvious However the dynamic nature of this function is not always appreciated Failure of one or both papillary muscles to shorten during the ejection phase of ventricular systole fibrosis, and atrophy of a papillary muscle or centrifugal migration of the papillary muscles due to left ventricular dilatation result in mitral incompetence Depending upon the etiology of the papillary muscle dysfunction apical systolic murmurs of varying characteristics may be heard. In general a noncontracting papillary muscle in a normal-sized heart is associated with a murmur which is late in onset and crescendo-decrescendo in quality whereas in the dilated heart the murmur is early beginning with the first heart sound and may be decrescendo plateau or crescendo-decrescendo in quality Obviously the murmurs of papillary muscle dysfunction may vary considerably depending upon the nature of the dysfunction and time course of activation of the muscle and other portions of the ventricular musculature. Associated electrocardiographic abnormalities may also occur

Mitral insufficiency due to acquired or congenital valvular disease has been exhaustively studied On the other hand mitral insufficiency secondary to disease of the papillary muscles has been almost completely neglected. Nevertheless, since our description of the *papillary muscle* syndrome in 1963 more than 20 papers dealing directly or indirectly with this syndrome have appeared In the present review we have extended the original description of the papillary muscle syndrome to include a number of diseases which either clinically or at necropsy have been *implicated in* the production of papillary muscle dysfunction in the hope that attention will be focused on those

diseases, in addition to circulatory insufficiency which may result in papillary muscle dysfunction

REFERENCES

1 Burch G E DePasquale N P and Phillips J H Clinical manifestations of papillary muscle dysfunction, Arch I t. Med. 112 112, 1963.
2 Phillips, J H Burch, G E and DePasquale, N P The syndrome of papillary muscle dysfunction Its clinical recognition, Ann Int. Med 59:508 1963
3. Phillips, J H DePasquale N P and Burch, G. E. The electrocardiogram in infarction of the anterolateral papillary muscle, AM HEART J 66:338, 1963
4. Estes, E. H J Dalton F M E tman, M L Dixon, H B., II and Hackel, D B. The anatomy and blood supply of the papillary muscles of the left ventricle AM. HEART J 71:356 1966.
5 Brock, R. C. The surgical and pathological anatomy of the mitral valve, Brit. Heart J 14:489 1952.
6. Chiechi, M A., Lees, W M and Thompson R. Functional anatomy of the normal mitral valve J Thoracic Surg 32:378, 1956
7 Rushmer R F Finlayson, B. L and Nash, A A Movements of the mitral valve Circulation Res 4:337 1956.
8 Davila, J C., nd P lmer T E The mitral valve, Arch Surg 81 174 1962.
9 Brockman, S K. Mechanism of the movements of the atrioventricular valves, Am J Cardiol 17:682 1966.
10 Burch, G. E and DePasquale, N P Time course of tension in papillary muscles of the heart J A M A 192 701 1965
11 Puff von A Barrenberg M and Goerttler T Röntgenkinematographische Untersuchungen uber den Bewegungsmechanismus der Mitralklappe Fortschr Geb Rontgenstrahlen. 102 607 1965
12. Burch, G E Ra C T and Cronvich J A. The George Fahr Lecture Certain mechanical peculiarities of the human cardiac pump in normal and diseased tates, Circulation 5:504, 1952.
13. DePasquale N P nd Burch, G. E The necropsy incidence of gross scars or acute infarction of the papillary muscles of the left entricle Am. J Cardiol. 1 169 1966
14 Ed ards, J E., nd Burchell, H. B. P thologic anatomy of mitral insufficiency Proc. Staff Meet. M yo Clin. 33 197 1958.
15. Smith H. L., Essex, H E., and Baldes, E. J A tudy of the movements of heart valves and of heart sounds, Ann. I t. Med. 33 1357 1950.
16. Actis-Dato, A. and Milocco, I Anomalous attachment of the mitral valve to the entricular wall, Am. J Cardiol. 1 :278, 1966.
17 Levy M J nd Ed ards, J E.: Anatomy of mitral insufficiency Progr Cardiovas. Dis. 5 119 1962.
18. Shone J D Seller R. D Anderson, R. C., Adams, P Jr Lillehei, C. W and Edwards, J E.: The developmental complex of parachute mitral valve, supravalvular ring of left trium, subaortic tenosis, and coarctation of aorta, Am. J Cardiol. 11 714 1963.
19 Van Buchem, F S P Arends, A. and Schroder E. A.: Endocardial fibroelastosis in adolescents and adults, Brit. Heart J 21:229 1959
20. Burch, G. E., nd Walsh, J J : Cardiac insufficiency in chronic alcoholism Am. J Cardiol. 6:864 1960.
21 Mattingly T W Clinical features and diagnosis of primary myocardial disease, Mod. Conc. Cardiovas Dis. 30:677 1961
22 Burch G. E and DePasquale, N P Viral myocarditis, Ciba Foundation Symposium on Cardiomyopathies, London, 1964 J & A. Churchill, Ltd., p. 376
23 Durrer D nd Tweel, L. H van der: Excitation of the left ventricular wall of the dog and goat, Ann New York Acad. Sc. 65 779 1957
24 Lev M The normal anatomy of the conduction system in man and its pathology in trioventricular block Ann. New York Acad. Sc. 111:817 1964
25. Smith, J C. Rupture of papillary muscle of the heart report of tw cases, Circulation 1 766 1950.
26. Robinson, J S., Stannard, M M and Long M. Ruptured papillary muscle after acute myocardial infarction, AM. HEART J 70:233, 1965.
27 Leatham, A. Auscultation of the heart Lancet 2 703 1958.
28. Phillips, J H. and Burch G E. Selected clues in cardiac auscultation, AM. HEART J 63 1 1962.
29 Burch G. E., and Phillips, J H Murmurs of aortic stenosis and mitral insufficiency masquerading as one another AM HEART J 66:439 1963.
30. Henke, R. P March, H W and Hultgren, H. N An aid to identification of the murmur of aortic stenosis with typical localization AM. HEART J 60:354 1960.
31 Vogelpoel, L., Nellen, M Swanepoel, A., and Schrire V The use of amyl nitrate in the diagnosis of systolic murmurs, Lancet 2:810, 1959
32. Shapiro, H. A., and Weiss, D R : Mitral insufficiency due to ruptured chordae tendineae simulating aortic stenosis New England J Med. 261:272, 1959
33. Case records of Massachusetts General Hospital, New England J Med 26 1033, 1962.
34 Osmundson, P J Callahan J A., and Edwards, J E. Mitral insufficiency from ruptured chordae tendineae simulating aortic tenosis, Proc. Staff Meet. May Clin. 33:235 1958.
35 Hollow y D H Whalen, R. E., and M I tosh, H D Systolic murmur developing after myocardial ischemia or infarction, J A.M A. 191 888 1965
36. Barlow J B and Bosman C. K : Aneurysmal protrusion of the posterior le flet of the mitral valve A an auscultatory-electrocardiographic syndrome AM. HEART J 71 166, 1966
37 Barlow J B.: Conjoint clinic on the clinical

significance of late systolic murmurs nd non-ejection systolic clicks, J Chronic Dis. 18:665 1965

38. H mphries, J O and M Kusick, V A.: The differentiation of organic nd innocent systolic murmurs, Progr Cardiovas. Dis. 5 152, 1962

39 Barlow J B Pocock, W A Marchand, P and Denny M. The significance of late systolic murmurs, Am. Heart J 66:443 1963.

40. Segal, B. L., and Likoff W Late sy tolic murmur of m tral regurgitation Am. Heart J 6 757 1964

41 T el, M E., Campbell, R. W and Zimmer J F Late systolic murmur nd mitral regurgitation, Am. J Cardiol 15 719 1966

42 Leatham, A. The alue of auscultation in cardiology Arch. I t. Med. 105:349 1960.

43 McKusick, V A. (ed.) Symposium on cardiovascular sound. II Clinical aspects, Circulation 16:414, 1957

44 Segal, B Kasparian, H., and Likoff W Mitral regurgitation in patient ith the Marfan syndrome Dis Chest 41:457 1962.

45. Bowers, D An electrocardiographic pattern associated with mitral valve deformity in Marf syndrome, Circulation 23:30, 1961

46. Reid, J V O Mid-systolic clicks, South African M J 35:353 1961

47 Bond, V F J Welfare, C. R Lide, T N and McMillan, R L. Perforation of interventricular septum following myocardial infarction, Ann. I t. Med 38 706, 1953

48. Harrison, R. J Shillingford, J P Allen, G. T and Teare, D Perforation of interventricular septum after myocardial infarction, Brit. M J 1:1066, 1961

49 Sanders, R. J Kern, W H and Blount, S. G., J Perforation of interventricular septum complicating myocardial infarction, Am. Heart J 51 736, 1956

50. Lee W Y Cardon, L and Slodki, S J Perforation of infarcted terventricular septum, Arch Int. Med. 109 731 1962.

51 Payne, W S., Hunt, J C and Kirklin, J W Surgical repair of entricular septal defect due to myocardial infarction, J A M.A. 183:603, 1963.

The treatment of cardiogenic shock

Part VI The search for an ideal drug

Leon I. Goldberg, Ph.D., M.D.
Atlanta, Ga.

Previous articles of this series have outlined the problems involved in determining the pathophysiological status of the patient in cardiogenic shock. It is unfortunate that in most cases we know very little about the precise physiological derangements in such patients and, accordingly, therapy must be empirical. The best we can do under these circumstances is to use a drug or combination of drugs whose actions would most likely correct the assumed physiological disturbances. Then, on the basis of success or failure, continue using the drug or try another with a different mechanism of action.

Faced with this less than optimal situation, the clinician can rationally make his choices only if he understands the pharmacology of the drugs he employs. Yet, as one reads the many publications concerning cardiogenic shock, it is apparent that many investigators have disregarded known pharmacological information and have grouped many dissimilar drugs in single classifications. Probably the greatest error which has occurred is to lump all sympathomimetic amines which raise blood pressure into one category, "vasopressor," regardless of whether the amines raise blood pressure by increasing cardiac output or by increasing peripheral resistance. Similar errors have occurred by inclusive use of the term "vasodilators." Drugs such as phenoxybenzamine, hydralazine, hexamethonium, and isoproterenol have often been grouped together under this classification. Because the results obtained with such dissimilar agents are frequently combined, it is often impossible to tell which agent (if any) has been beneficial.

This article is designed to present the pharmacological actions of several drugs now used in the treatment of shock in the hope that future investigators will be more aware of the differences in action of these agents. In this way, beneficial and detrimental actions may eventually be sorted out and a framework will be provided for more logical new drug development.

Sympathomimetic amines.[1-4] Over 300 sympathomimetic amines have been synthesized. Since only a handful of these have been used therapeutically, it is entirely possible that many of the discarded amines will have more clinically beneficial actions than those currently employed. This is true because the reasons for choosing a sympathomimetic amine for clinical trials has usually been based on the following properties: (1) potency to raise blood pressure and (2) long duration of action. Neither of these attributes are of value to the patient with cardiogenic shock. It is much

From the Division of Clinical Pharmacology, Department of Medicine, and the Department of Pharmacology, Emory University School of Medicine, Atlanta, Ga.
Many of the opinions expressed are based on research supported by grant [illegible], National Heart Institute, United States Public Health Service.

more desirable to have a drug which will improve cardiac output and even more important, one which will distribute the increased blood flow to areas which need it.

Sympathomimetic amines have four known types of action on the cardiovascular system (1) they may cause vasoconstriction by action on α-adrenergic receptors (2) they may cause vasodilation and cardiac stimulation by action on β-adrenergic receptors (3) they may exert α and β-adrenergic effects by causing release of norepinephrine from sympathetic nerves (indirect action) and (4) they may have cardiovascular actions unrelated to α- or β-adrenergic receptors. Most sympathomimetic amines will exert more than one of these effects. Which effect predominates varies not only among different animal species, but also upon differential actions in various organ systems in the same animal

There is a tremendous amount of information available concerning the relative action of these amines in experimental animals and in normal man. However extensive studies are needed to tell which actions will predominate in the patient in cardiogenic shock. The following description of the pharmacological actions of several sympathomimetic amines is presented with this limitation in mind

NOREPINEPHRINE (LEVARTERENOL, LEVOPHED) Norepinephrine acts directly on β-adrenergic receptors in the heart to cause cardiac stimulation and on α-adrenergic receptors in the arterial and venous systems to cause vasoconstriction Increase in cardiac contractility and vasoconstriction have been found to occur at approximately the same dose of the amine in both experimental animals and man. Because of these opposing actions the hemodynamic effects of norepinephrine will depend upon whether the increased pressure and positive inotropic effect produced by the drugs will increase flow or whether flow to a particular region will be decreased because of vasoconstriction It is obvious that the hemodynamic actions of norepinephrine will be variable in different patients with cardiogenic shock.

Norepinephrine also exerts a β-adrenergic action on peripheral blood vessels, but this occurs only at doses approximately 50 times that which stimulates α receptors. Accordingly peripheral vasodilation with norepinephrine can usually be seen only after administration of large doses of α-adrenergic blocking agents. It has been suggested however that β-adrenergic peripheral vasodilation may be a factor in the hypotensive state which occurs after prolonged norepinephrine infusion Norepinephrine also may cause vasodilation by a reflex mechanism but again this action is masked by the intense α-adrenergic vasoconstriction This mechanism also has been invoked to explain postnorepinephrine infusion hypotension.

EPINEPHRINE (ADRENALIN SUPRARENIN) Epinephrine acts directly on β-adrenergic receptors in the heart to cause cardiac stimulation. Its action on peripheral vessels, however is more complex in that both α- and β-adrenergic receptors are activated at approximately similar dose levels. In usual clinical doses, the β-adrenergic vasodilation predominates and total peripheral resistance usually decreases. However it is important to emphasize that the α-adrenergic action is still present and vasoconstriction may occur in renal vessels. Therefore, although cardiac output may increase, much of the increase in blood flow is directed to the skeletal muscles and renal blood flow may actually be markedly reduced Epinephrine also causes reflex vasodilation but again this action is masked by the predominate α- and β-adrenergic effects.

ISOPROTERENOL. Isoproterenol in usual clinical doses has only β-adrenergic actions and causes cardiac stimulation and peripheral vasodilation in approximately equal doses. As with epinephrine some of the increase in blood flow is diverted to skeletal muscles, but mesenteric blood flow also increases. Most studies in normal man and experimental animals indicate that renal blood flow does not increase. The lack of increase in renal blood flow after intravenous administration of isoproterenol does not mean that there is an absence of β receptors in the renal vascular bed for administration of isoproterenol into the renal artery will cause renal vasodilation. The difference in the results of intraarterial and intravenous injection may be related to the fact that when isoproterenol reduces

peripheral resistance powerful vasoconstrictor reflexes occur which could predominate in the renal vessels over the relatively weak β-adrenergic vasodilation. The β-adrenergic effect on skeletal muscle is much more intense and is not greatly reduced by reflex constriction. Reflex vasoconstriction may also be important in the action of isoproterenol on the veins. The effect of isoproterenol on veins has been the subject of much debate but recent work suggests that the drug does act on β receptors in veins to cause dilation. Again however reflex vasoconstriction may predominate Reflexes related to decreased peripheral resistance may also add to direct effects of isoproterenol to produce tachycardia.

METARAMINOL (ARAMINE) Metaraminol is classified as an indirect acting sympathomimetic amine in that its actions are considered to be due to release of norepinephrine The hemodynamic actions of this amine are very similar to those of norepinephrine but are of much longer duration Because it is acting at least in part by release of norepinephrine it is possible that the effects of the drug may be attenuated in patients who have reduced catecholamine stores following prolonged therapy with reserpine or guanethidine The clinical implications of this finding are debatable but would suggest that in the event of lack of responsiveness to metaraminol a direct acting sympathomimetic amine should be substituted

MEPHENTERMINE (WYAMINE) Mephentermine is also an indirectly acting sympathomimetic amine which exerts β-adrenergic effects on the heart and α-adrenergic actions on the peripheral vessels. It has often been stated that mephentermine is a pure β-agonist and is therefore pharmacologically equivalent to isoproterenol. Studies in both experimental animals and man however do not support this conclusion Unlike isoproterenol injection of mephentermine into peripheral vessels of animals causes vasoconstriction which is blocked by α-adrenergic blocking agents Furthermore clinical studies have demonstrated that mephentermine may increase peripheral resistance and reduce heart rate[3] much the same as norepinephrine and unlike isoproterenol The vasoconstrictor properties of mephentermine do appear to be less in the patient in shock than those of metaraminol and norepinephrine.

METHOXAMINE (VASOXYL) Methoxamine is a direct acting amine which has only α adrenergic activity in usual clinical doses. Because it produces vasoconstriction without concomitantly causing cardiac stimulation administration of methoxamine increases the work of the left ventricle and elevates left and right atrial pressures. Large doses of this amine have been shown to produce pulmonary edema in animals. It would therefore appear that this drug has no place in the treatment of cardiogenic shock.

PHENYLEPHRINE (NEO SYNEPHRINE) Phenylephrine is very much like methoxamine in that its predominate action is on α-adrenergic receptors to cause vasoconstriction β-adrenergic action to stimulate the heart however can be demonstrated with the amine when administered in large doses to experimental animals or when applied to the isolated heart. This β-adrenergic effect is not usually apparent in clinical doses and is probably of limited value in the treatment of cardiogenic shock.

DOPAMINE Dopamine is the most recent sympathomimetic amine introduced for the treatment of shock.[4] Studies in our laboratories during the past several years have demonstrated that dopamine has an unusual action to increase renal blood flow by direct vasodilating action on the renal vascular bed [7,8] This vasodilation is different from that produced by amines such as isoproterenol since this effect of dopamine is not blocked by β-adrenergic blocking agents.[9] In addition to nonadrenergic renal vasodilation dopamine produces cardiac stimulation by a β-adrenergic action and skeletal muscle vasoconstriction by an α adrenergic action. Hemodynamic studies in normal subjects and patients in shock have demonstrated that dopamine increases cardiac output and usually reduces total peripheral resistance Unlike isoproterenol dopamine can produce substantial increments in cardiac output without producing tachycardia [4] The reason for the difference is not entirely clear for the β-adrenergic mechanism responsible for the direct cardiac stimulation produced by both amines appears to be identical [4] Studies in the dog suggest

that the difference in tendency to produce tachycardia is probably related to the fact that dopamine exerts a reflex effect which opposes an increase in heart rate due to reduction in total peripheral resistance. Isoproterenol on the other hand produces a more pronounced reduction in total peripheral resistance and reflex tachycardia is unopposed Repeated observations have demonstrated that dopamine consistently increases renal blood flow whereas renal blood flow with isoproterenol usually does not increase On the other hand although both amines have the ability to dilate the mesenteric vascular bed preliminary data in the dog indicates that isoproterenol increases mesenteric blood flow more than dopamine. It is clear then that although both isoproterenol and dopamine reduce total peripheral resistance they should not be considered as identical "vasodilators."

There is insufficient data to conclude whether administration of isoproterenol or dopamine will be more beneficial for the patient in cardiogenic shock. Both drugs have been found to increase cardiac output in such patients and administration of each of the amines has produced marked clinical improvement in some patients. Since isoproterenol and dopamine are administered intravenously and since both amines have a relatively short duration of action, comparative studies in the same patient should be feasible

α Adrenergic blocking agents The use of α-adrenergic blocking agents in the treatment of shock is based on the hypothesis that intense vasoconstriction due to release of norepinephrine from sympathetic nerves and norepinephrine and epinephrine from the adrenal medulla is responsible for perpetuation of the shock state. Since α-adrenergic blocking agents prevent this vasoconstriction without affecting the cardiac stimulation produced by these amines, they have been advocated for the treatment of shock. Two α-adrenergic blocking agent have been used the long lasting blocking agent phenoxybenzamine (Dibenzeline) and the shorter-acting phentolamine (Regitine) Phenoxybenzamine has been more generally used primarily because of its long duration of action and since it does not exhibit tolerance which occurs with phentolamine

There has been little data to suggest that α-adrenergic blocking agents are beneficial when administered as the sole agent for the treatment of patients with cardiogenic shock. These drugs may be more appropriate for patients who have a relatively normal myocardium and are in shock because of prolonged blood loss or infection The reason for not advocating α-adrenergic blocking agents in cardiogenic shock is that the blocking of vasoconstriction will not improve cardiac function and if the myocardium is impaired severe hypotension may occur To correct this situation it has been suggested that phenoxybenzamine or phentolamine be used concomitantly with β adrenergic stimulating drugs such as norepinephrine.[13] When this is done the vasoconstrictor component of norepinephrine is blocked and the β-adrenergic effect predominates. Although this may be a useful procedure it is not easy to carry out since the amount of the α-adrenergic blocking agent needed to prevent the vasoconstriction produced by norepinephrine may vary considerably from patient to patient. Phenoxybenzamine has also been tried with dopamine in the hopes of blocking vasoconstrictor effects of the kidney produced by circulating catecholamines and to attenuate the α-adrenergic effects of large doses of dopamine Studies in the dog have suggested that this combination could be useful[14] Preliminary studies in our laboratory with the combination of phenoxybenzamine and isoproterenol however have suggested that the combined use of these agents may be detrimental When they are used together isoproterenol may not increase cardiac output, presumably because of the marked venous pooling resulting from the block of reflex vasoconstriction in the veins

Corticosteroids The efficacy of corticosteroids in the treatment of cardiogenic shock is unproved This does not mean that adrenal corticosteroids may not have beneficial actions, but it is most difficult to obtain positive data from reported clinical studies. Animal experiments suggest that large doses of corticosteroids have a vasodilating action and also possibly cardiac stimulating action. Furthermore there are suggestions that large doses of these drugs may potentiate the

action of sympathomimetic amines. At present there does not appear to be any reason why these drugs should be given or any reason why they should not.

Conclusions

There is no ideal drug for the treatment of cardiogenic shock. The most appropriate therapy today appears to be one of the sympathomimetic amines with β-adrenergic cardiac stimulating properties. The choice for initial therapy must be made between (1) amines such as norepinephrine and metaraminol which cause generalized (α-adrenergic) vasoconstriction in addition to cardiac stimulation, (2) isoproterenol which exerts β-adrenergic activity to stimulate the heart and to cause vasodilation especially in skeletal muscle and mesenteric vessels, and (3) amines whose spectrum of actions are different from (1) and (2). Today it would seem reasonable to initiate therapy with isoproterenol. If the patient tolerates the tachycardia and if blood pressure is adequate for perfusion of vital organs, this amine may be continued. If not one of the amines with vasoconstrictor and cardiac stimulating properties should be substituted immediately.

Dopamine represents a new experimental approach since in addition to β-adrenergic cardiac stimulating properties and weak α-adrenergic vasoconstricting properties this amine causes nonadrenergic vasodilation of the renal blood vessels. Dopamine has potential advantages over isoproterenol in that it has less of a tendency to cause tachycardia and may produce a greater increase in renal blood flow. α-adrenergic blocking agents have potential beneficial actions to block vasoconstriction by endogenously and exogenously administered sympathomimetic amines. The combined use of these drugs with norepinephrine or dopamine may be helpful in some patients.

It must be emphasized that proper utilization of any of the above drugs should not take precedence over proper expansion of plasma volume, correction of electrolyte imbalances and acidosis, and treatment of arrhythmias, since these procedures alone may be effective in combating shock. Unless these preliminary maneuvers are carried out, sympathomimetic amine therapy will probably be ineffective.

It is difficult to predict the direction new pharmacological research should take. The example of dopamine may provide a clue for discovery of more selective agents which can be used to correct specific physiological derangements. Ultimately, the ideal drug may be one which selectively dilates various regional beds since cardiac function during the shock state may be assumed by a mechanical pump in the not too distant future.

REFERENCES

1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: Heart force effects of sympathomimetic amines as a basis for their use in shock accompanying myocardial infarction, Circulation 8:883, 1953.
2. Goldberg, L. I., Bloodwell, R. D., Braunwald, E., and Morrow, A. G.: The direct effects of norepinephrine, epinephrine and methoxamine on myocardial contractile force in man, Circulation 22:1125, 1960.
3. Goldberg, L. I., and Dorney, E. R.: Treatment of shock following myocardial infarction. Diverse actions of drugs used, Postgrad. Med. 37:152, 1965.
4. Eckstein, J. W., and Abboud, F. M.: Circulatory effects of sympathomimetic amines, Am. Heart J. 63:119, 1962.
5. Brofman, B. L., Hellerstein, H. K., and Caskey, W. H.: Mephentermine—an effective pressor amine, Am. Heart J. 44:396, 1952.
6. MacCannell, K. L., McNay, J. L., Meyer, M. B., and Goldberg, L. I.: The use of dopamine in the treatment of hypotension and shock, New England J. Med. 275:1389, 1966.
7. McNay, J. L., McDonald, R. H., Jr., and Goldberg, L. I.: Direct renal vasodilation produced by dopamine in the dog, Circulation Res. 16:510, 1965.
8. McDonald, R. H., Jr., Goldberg, L. I., McNay, J. L., and Tuttle, E. P., Jr.: Effects of dopamine in man. Augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow, J. Clin. Invest. 43:1116, 1964.
9. McNay, J. L., and Goldberg, L. I.: Comparison of the effect of dopamine, isoproterenol, norepinephrine, and bradykinin on canine renal and femoral blood flow after POB, J. Pharmacol. & Exper. Therap. 151:23, 1966.
10. McDonald, R. H., Jr., and Goldberg, L. I.: Analysis of the cardiovascular effects of dopamine in the dog, J. Pharmacol. & Exper. Therap. 140:60, 1963.
11. Black, W. L., and Rolett, E. L.: Dopamine-induced alterations in left ventricular performance, Circulation Res. 19:71, 1966.
12. Wilson, R. F.: Combined use of norepinephrine and Dibenzyline in clinical shock, S. Forum 12:30, 1961.
13. McNay, J. L., and Goldberg, L. I.: Hemodynamic effects of dopamine in the dog before and after alpha adrenergic blockade, Circulation Res. 18:I-110, 1966.
14. MacCannell, K. L., McNay, J. L., Clifford, R. R. M., and Haas, J. A.: Unpublished observations.

Annotations

Interrelations of cardiac necrosis acute hypotension, and ventricular fibrillation

Histologically the microscopic changes in heart tissues produced by intracoronary injection of hexachlorotetrafluorobutane (hexa) resemble those observed in clinical coronary infarction.

I tracoronary injection of Hexa in nonthora cotomized dogs results in an early and marked hypotension bradycardia, decrease in total peripheral resistance (TPR) and fall in cardiac out put (CO). The upward deflection of the first deriv t of the left ventricular pressure pulse dP/dt (max.) increases briefly for 10 t 20 seconds and then falls progressively The downward deflection dP/dt (min) falls early nd progressively Experiments have been followed for one hour

The hemodynamic responses are due to Bezold type reflex (BTR), arising in the left ventricular wall, tra eling centripetally through the vagus nerve and reflexly expressing its action as an inhibition of the motor sympathetic outflow since the bradycardia is not blocked by methylatropine.

Single fiber afferent preparations of the cervical vagus nerve, originating in the infarcted area, show characteristic changes in pattern of firing coincid ng w th these responses following intra coronary injection of Hexa. Pattern of potentials, length of burst of activity of group of action potentials, as well as changes in rat of impulses per unit of time in the sensory vagus may all have role in the information which is transmitted from cardiac receptors t the site of infarction to the central nervous system These changes may con tribut to the decrease i entropy or randomness which constit tes increase in information carried centrally Thus, there could be different reflex results on the motor side as result of varying information carried to centers. As an example in the control period, it is most often observed that each single left entricular pressure pulse is related t an early nd lat burst of activity in the fibers of the agus hich originat from receptors in the left entricle these tw bursts are separated by brief silent period (randomness or entropy). Under these control circumstances little information is being carried centrally

I farction by intracoronary Hexa increases rate of firing decreases total duration of burst of afferent agal action potentials, nd fuses the tw separate action potential bursts of activity (related t one cardiac cycle) noted in the control period into single period of activity associated with one left ventricular pressure pulse. This type of information carried centrally produced a BTR bradycardia (decreased sympathetic activity), hypotension decreased CO and TPR, peripheral vasodilation. On the other hand, intracoronary epinephrine slightly increases the rat but shortens the duration of each of the two bursts in a control single heart cycle Differing from Hexa, intracoronary epinephrine never fuses the tw control bursts of any cy le In theory this latter type of information transmitted centrally could result in a different kind of response from that produced by Hexa, intracoronary epinephrine being characterized by strong motor vagal activity and resultant peripheral vasoconstriction reflexly from baroreceptors as blood pressure falls.

It should be emphasized that intracoronary epinephrine is given in very small doses resulting only in an increased entricular action which stimulates myocardial receptors and that there is no direct systemic action of epinephrine in these doses. Stimulation of cardiac receptors by intracoronary epinephrine may be considered to reflexly activate motor vagus fibers (Bezold reflex) which act as a vagal brake on excessive ventricular rates and force.

The BTR appears t be related to the myocardial necrosis produced by Hexa. Usually Bezold reflexes cannot be demonstrated when coronary obstruction is produced by intracoronary injection of inert substances or by ligation with an open-thorax preparation although brief BTR has been clearly described by Costantin.

There are several factors participating in the acute hypotension observed after myocardial necrosis due to intracoronary injection of Hexa, addition to those related to BTR. These are myocardial necroses leading to a decrease in the force of contraction, local release of myocardial catecholamines causing brief initial increase in dP/dt (max), and baroreceptor compensatory re sponses activated by the tendency for blood pressure to fall (Table I).

An attempt was made to individualize these

Supported by Grants HE 10771-01 HE 08041-13 HE 08 367-08, and HE 08084-03 from the National Heart Institute, United States Public Health Service

*Bezold type because the card ac component is resulting to stimulus which is not true in the Bezold reflex.

Table I Factors in acute hypotension of cardiogenic origin

Model	Factors concerned in acute hypotension after infarction	Factors absent	Reason factors are absent	Equal MEW post infarction	Ventricular fibrillation (VF)	Special consideration
Normal	Bezold type reflex Myocardial necrosis Release local NE Compen. baro.		Compen. baro. overridden by BTR	BP lower (BTR present) CO higher	Incidence high temporal dispersion of recovery of excitability permit re-entry	Low post infarct press., low O₂ need for MEW Physiologic reason for BTR: P work requires more energy than V work
Vagotomized	Myocardial necrosis Release local NE Compen. baro.	BTR	Sensory limb of reflex arc is cut	BP higher (BTR absent) CO lower	Incidence VF low BTR absent, little or no temporal dispersion of recovery of excitability no re-entry	TPR increase IN nervo intact fall in BP causes reflex + TPR BP may be higher after infarction
Reserpinized	Myocardial necrosis	BTR Release local NE Compen. baro.	Motor mediator of reflex depleted cardiac tissue NE depleted	BP lower (NE depleted) CO higher (BTR absent)	Incidence VF low BTR absent little or no temporal dispersion of recovery of excitability no re-entry NE also absent	Low post infarction press. low O₂ need for MEW Physiologic reason for BTR, P work requires more energy than V work
Atropinized	BTR Myocardial necrosis Release local NE Compen. baro.	Vagal motor activity	Motor vagus not concerned	BP higher CO lower	Incidence high temporal dispersion of recovery of excitability permits re-entry	Bradycardia of BTR is prevent d Increase in TPR later than first 10 min block of cholinergic vasodilators

*Compensatory baroreceptor reflexes

factors by producing standard myocardial lesion with i tracoronary injection of Hexa in vagotomized, reserpinized and tropinized animals as well as i normal ones. Vagotomy by interfering w th the aff rent path ay of the BTR would characterize responses t m ocardial damage release of c techolamines, and compensatory baroceptor responses. I prereserpinized nimals only the myocardial damage would be evident. This is true because these imals are depleted of catecholamines hence the BTR is not present since there is little or no sympathetic mediator to influence the myocardial target cell nd also there is an inability t release local tissue norepinephrine Normal nimals, on the other hand would hav BTR myocardial damage compensatory baroceptor activity and local release of catecholamines t the time of Hexa infarction.

Statistical tudies of those four groups show that early pressure changes are small and not significa t in the groups here BTR is absent (agotomized nd reserpinized). A short lived increase i dP/dt (ma) is present in those groups where there is techolamine release t the time of infarction (intact agotomized, tropinized). Decreases in dP/dt (m) and f ll i CO are common to ll groups nd correlat ith myocardial damage Changes i TPR and i dP/dt (max.) correlat ith BTR and hanges in motor sympathetic activ ty *Control* nimals in which potent BTR t the time of infarction is present, overriding carotid si us, and aortic arch baroceptor activity exhibit early and marked fall blood pressure nd CO and decrease in II R dP/dt (max. + min.) decreases throughout the hour of observ tion after short li ed increase dP dt (max.) t the time of infarction. I *gotomized* mals ith no BTR originating in receptors the heart but with increased motor sympathetic activ ty through reflex (carotid si us) baroceptor action increase TPR to nearly double the control alue after infarction dP/dt (max.) increases t the time of infarction but this incre se last more tha 10 minutes. Tachy cardia instead of brad ardia is ually present Surprisingly *atropinized* animals, lthough BTR is present beha similarly (after the first 10 minutes after infarction) t togomized animals (no BTR) th respect t TPR. However brady ardia (decre sed motor ympathetic acti ty) and fall of dP/dt (ma) are present as in case of *ent al* animals (act BTR). It is possible that atropine bl ks sympathetic cholinergic asodilator fibers related t hanges in TPR. These cholinergic sympathetic fibers participat in pressure-regulating reflexes as ll as psy hogenic pressure responses.[12]

Myoc rdial extern l work as det rmined in ample of 10 animals chosen t random from each group. Myocardial external ork (MEW) per minute per kilogram of body eight aries in ach group in the preinfarction period. However t the end of one hour MEW all infarcted groups is remarkabl similar Pos farction intact nimals th activ BTR nd reserpinized nimals with no activ baroceptor reflexes, since the motor sympathetic mediator is depleted, demonstrat that for equiv lent mou t of ork blood pressure is lower nd CO is relati ly higher than in tropinized and vagotomized animals. C nsequentl my cardial O consumption in these normal and reserpinized animals is less. V lume ork is done t less expense i O_2 use than is pressure work. It is suggested that BTR after infarction may be useful, since by overriding the baroceptor activity nd lowering the blood pressure in normal animals, it permit high CO for eq ivalent amount of work (oxygen use).

Vagotomized nd reserpinized imals ha significantly lower incidence (11 and 14 per cent respecti ely) of tricular fibrillation (VF) than i tact or tropinized animals (45 and 37 per cent) lthough micro and macro lesions are similar It is possible that local tissue rele se of c techolamines and changes in activity in motor mpathetics due t BTR are importa t in the production of VF in these experiments.

Ischemic areas increasingly faster ectopic entricular activ ty local rele se of myocardial catecholamines, nd increase or decrease of myocardial c techolamines at nerve end due t hanges in motor sympathetic activity fa or VF by increasing the temporal dispersion of recovery of excitability[13] and facilitating re-entry The low incidence of VF in vagotomized and reserpinized animals suggests that the rele se of myocardial catecholamines and changes i motor sympathetic act ity (BTR) play an important role i the development of this ventricular arrh thmia. BTR t the time of Hexa infarction ppears t be more important. Incidence f VF is low i agotomized (no BTR) but th sig ificant release of techolamines t the time of infarction (incre se i dp/dt (max.) Reserpinized animals ha e neither BTR (motor mediator depleted) nor local tissue techolamines.

BTR may be helpf l in relat on t work requirements of the myocardium but deletrious in re spect t incidence of entricular fibrillation.

Fra k Barrera M.D
G ido Isc io M D
Thongchair Kolatat M D
Ronald J Tala ida Ph D
M J Oppenheimer M.D
Temple U ersity School f Med ine
Departments of Physiology nd Pharmacolog
3400 N Broad St.
Philadelphia P 19140

*Chilean Medical Board Fellow 1963 66, Department of Ph si ology Temple University School of Medicine

**Special Fellow United States Public Health Service N 1 F3 GM 21,311-01.

REFERENCES

1. Ascanio, G Barrera, F La tsch, E. A nd Oppenheimer M J Role of reflexes f llowing myocardial necrobiosis, Am J Physiol 209: 1081 1965
2. Kolat t T Ascanio, G Tallarida, R J nd Oppenheimer M J Action potentials in the sensory vagus t the time of coronary infarction, Am. J Physiol. 213 71 1967
3. Brillouin, L Ph ical entropy nd information, J Appl. Physiol. 22 338, 1951

4. Brillouin, L. Science and information theory, ed. 2, New York, 1962, Academic Press, Inc.
5. Mackay, D. M., and McCulloch, W. S. The limiting information capacity of a neuronal link, Bull. Math. Biophys. 14:127, 1952.
6. Shannon, C. E. The mathematical theory of communication, Urbana, 1949, Univ. Illinois Press.
7. Sleight, P., and Widdicombe, J. G. Action potentials in fibers from receptors in the epicardium and myocardium of the dog's left ventricle, J. Physiol. (Lond.) 181:235, 1965.
8. Costantin, L. Extracardiac factors contributing to hypotension during coronary occlusion, Am. J. Cardiol. 11:205, 1963.
9. Barrera, F., Ascanio, G., Lautsch, E. V., and Oppenheimer, M. J. Factors in acute hypotension and ventricular fibrillation after cardiac necrosis, Am. J. M. Sc. 253:71/675, 1967.
10. Burn, J. H. Effect of psychopharmacological drugs on the circulation, in Handbook of physiology, Sec. 2, Circulation, Washington, D. C., 1965, American Physiological Society, Vol. III, p. 2450.
11. Barrera, F., Ascanio, G., Bourtwell, J. H., P nla, M. P., and Oppenheimer, M. J. Importance of myocardial catecholamines in myocardial infarction, Am. J. M. Sc. 252:77/177, 1966.
12. Abboud, F. M., and Eckstein, J. W. Reflex vasoconstrictor and vasodilator responses in man, Circulation Res. 18 (Suppl. 1): I-96, 1966.
13. Uvnäs, B. Central cardiovascular control, in Handbook of physiology, Sec. 1, Neurophysiology, Washington, D. C., 1960, American Physiological Society, Vol. II, p. 1131.
14. Sarnoff, S. J., Braunwald, E., Welch, G. H., Jr., Case, R. B., Stainsby, W. N., and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index, Am. J. Physiol. 192:148, 1958.
15. Han, J., and Moe, G. K. Nonuniform recovery of excitability in ventricular muscle, Circulation Res. 14:44, 1964.

A new approach to studies of the fibrinolytic enzyme system in man

More than 100 years ago Rokitansky propounded the hypothesis that deposits of intimal fibrin were the initiating lesions of arteriosclerosis. This concept remained neglected for many years following the work of Virchow, who considered that disturbed lipid metabolism was the relevant etiologic factor in the pathogenesis of this disease. Rokitansky's thrombogenic hypothesis was revived by Duguid[1] in 1946 when he observed the deposition of mural thrombi which were subsequently covered by endothelium and thus incorporated into the vessel wall. These findings have been partially confirmed, so that in recent years there has been a renewed interest in the thrombogenic theory of arteriosclerosis. While the protagonists of this theory recognize that important constituents of these mural thrombi are platelets and leukocytes, it is generally agreed that fibrin is also present.

The fibrinolytic enzyme system is believed to be concerned with the enzymatic dissolution of fibrin in vivo. Plasmin is the proteolytic enzyme responsible for fibrinolysis and is derived by the action of plasminogen activators on the stable precursor plasminogen which is present in the globulin fraction of plasma. Plasmin is a relatively nonspecific proteolytic enzyme, but selectivity for fibrin is obtained by a high concentration of circulating inhibitors (antiplasmins) and the absorption of plasminogen activator into fibrin deposits in which sufficient plasminogen is assumed to be available to effect intrathrombi fibrinolysis.

The existence of some form of a dynamic equilibrium between fibrin deposition (coagulation) and its removal (fibrinolysis) has been postulated by many workers over the past half century, but in 1956 Astrup[2] further elaborated this concept by suggesting that coagulation and fibrinolysis were normal and continuous physiologic phenomena on the intimal surface of the vessel walls. Although there is some impressive evidence in favor of this hypothesis it remains, as yet, unproved. Despite this, however, it has generated considerable research endeavor, for Astrup further postulated that a breakdown of this dynamic equilibrium by uncompensated shifts of either coagulation or fibrinolysis could lead to hemorrhagic diathesis on the one hand or thrombosis on the other. Thus in the light of the thrombogenic theory of arteriosclerosis, a defective fibrinolytic mechanism could be relevant etiological factor.

Subsequent efforts by many groups of investigators using single sample analytic techniques to demonstrate low levels of fibrinolysis in patients with occlusive vascular disease have proved to be both disappointing and controversial. In a review of the recent literature Fearnley has concluded that there is little evidence of a difference in blood fibrinolytic activity between men with overt coronary artery

disease and age-matched controls, but there is some reason to suspect defective fibrinolysis in postmenopausal women, in women with ischemic heart disease, and in persons of both sexes who suffer from peripheral arteriosclerosis.

There are many reasons for the present uncertainty. Not least of these are the methodologic differences that exist among laboratories and also the assumption that in vivo thrombolysis is necessarily a simple function of the absolute level of circulating plasminogen activator. There is evidence to suggest that the level of circulating plasminogen activator can fluctuate, in any one person, from day to day and throughout the same day. Thus, unless extreme and prolonged differences exist between patients with occlusive vascular disease and the controls, comparison by single estimations could fail to provide satisfactory information. Furthermore, if the fibrinolytic enzyme system is in a state of dynamic flux incorporating a complex system of activation and inhibition feedback controls, then the interpretation of an isolated random absolute level of plasminogen activator could prove to be impossible, for a low level might indicate either an uncompensating fibrinolytic system, that the static mechanisms were set low due to a diminished level of fibrin deposition, or that active thrombolysis was in fact taking place in association with low levels of effective fibrinolytic inhibition—either systemically or locally within the thrombus. Finally, until a quantitative measure of the actual level of in vivo fibrin deposition and removal is available, then it will continue to be difficult to interpret any information gained from studies based upon the present assay techniques.

Certain physiologic activities such as exercise are believed to stimulate an increase in the activity of both coagulation and fibrinolytic mechanisms.[14-16] It seemed possible that if this stimulant could be standardized then it would be feasible to study the dynamic equilibrium in a more appropriate way than by the method of single sample analysis. Present methodologic limitations necessitated a restriction of the study to the capacity of the individual to generate circulating plasminogen activator, and it was also necessary to assume that, at least in this acute situation, an increase in plasminogen activator was the single most important factor governing in vivo thrombolysis. The search, therefore, was for a group of subjects whose capacity to generate circulating plasminogen activator to a standardized fibrinolytic stimulant appeared to be defective. There was a good precedent for such an investigation: careful analysis of previous exercise fibrinolysis studies revealed that some subjects responded poorly. Those who have commented on these poor responders have explained them on the basis of increased physical fitness, inappropriate timing of postexercise blood samples, and the occurrence of an unusual reaction to stress. In fact, it is difficult to come to any satisfactory conclusions on the reality of this phenomenon because of the variations in fibrinolytic assays and the types of exercise used in the different laboratories and, most significant of all, because no attempt was made to ascertain whether this phenomenon was reproducible.

The first study carried out in this pilot project was on a group of 50 healthy volunteers (25 male and 25 female) aged between 18 and 30 years (mean age, 22.3 years). Cubital venous blood samples were obtained before and immediately after a standard treadmill exercise procedure (8 minutes at 3.4 m.p.h. at 5° elevation). The level of plasminogen activator was assayed by the euglobulin lysis time and the percentage fibrinolytic response recorded as A − B/A × 100, where A and B represented the pre- and postexercise euglobulin lysis times respectively. All subjects were studied on at least two occasions. The results of this investigation have been described in detail elsewhere; they demonstrated (1) that the fibrinolytic response to the exercise procedure was reproducible in any one individual, (2) that there was a significant difference in response between individuals, and (3) that it was possible to isolate a small group whose response was consistently poor. It was also noted that there were no poor responders in the female group, and statistical analysis revealed the young women to be significantly better responders than the men.

Although there was no correlation between the pulse rate and fibrinolytic responses to the exercise procedure, it was concluded that the individual variability of fibrinolytic responses could be explained on the basis of the variability of stress of the exercise on different individuals which was not apparent from the pulse rate responses. Moderate exercise stimulates the release of circulating epinephrine and there appears to be an individual variation in the amount produced. Epinephrine is a powerful fibrinolytic stimulant, and it was argued that the variation in fibrinolytic response could be related directly to the quantity of epinephrine released. At the time in which these experiments were conducted no facilities for the measurement of blood catecholamines were available in Edinburgh. Accordingly a more indirect and less physiologic approach was made in which 25 of the young healthy volunteers already studied on the treadmill were given a standard dose of intravenous epinephrine (10 μg per 1.95 square meter of surface area per minute) for 2 minutes in 20 ml. of saline. Cubital venous blood samples were obtained before and 2 minutes after the epinephrine infusion at the peak level of circulating plasminogen activator. All the volunteers were subjected to at least two epinephrine infusions at weekly intervals. The results clearly demonstrated a statistically highly significant correlation between the fibrinolytic response of an individual to exercise and intravenous epinephrine. It was assumed, therefore, that the variation in fibrinolytic response to exercise between individuals could not be explained entirely on the basis of individual variability of epinephrine production and that there was indeed a small group of persons whose mechanisms for the release of plasminogen activator to stress appeared to be defective.

Despite these findings it was felt that the definition of a poor responder was too restrictive to be of pathophysiologic significance, in the sense that the fibrinolytic stimulants were both submaximal and of relatively short duration. Thus given a more severe and/or prolonged stimulus, the so-called

poor responders would be indistinguishable from their colleagues. Further experiments were carried out to test this hypothesis and the results clearly demonstrated that the poor responders to the moderate exercise and epinephrine procedures continued to show impaired responses when submitted to a 4 m t exhausti treadmill exercise procedure and one in which the exercise was continued for 3 to 5 hours, during which time the subjects walked at least 12 miles.[26]

Throughout the study of these young subjects the demonstration of individual reproducibility of fibrinolytic response to the exercise procedure had been so impressive that it was assumed that the ability to generate plasminogen activator to exercise was in part genetically determined. However, attention was turned to the effect of environmental factors on this phenomenon following the study of one subject who, during the period of investigation transformed from a good to a poor responder, remained so for some weeks, and then returned to what was believed to be his norm. Subsequent inquiries revealed that the period of poor fibrinolytic response to the moderate exercise procedure coincided with a tragic episode within the subject's family. On the basis of this fortuitous and somewhat tenuous information a small pilot study was instigated in order to examine in more detail the effects of prolonged mental stress on the fibrinolytic response to exercise. Accordingly, the fibrinolytic response to the moderate exercise procedure was studied in five male medical student volunteers before, during and after a recent University degree examination, the results of which were recognized to have profound effects on whether the candidates would be permitted to continue their medical studies. The control group consisted of five age matched medical students enjoying their summer vacation. The results of this study demonstrated that three of the examination candidates, whose fibrinolytic response several days prior to the examination had been satisfactory, immediately before or during the examination period, failed to respond, whereas the remaining two showed no such deterioration.[26] Collateral fibrinolytic assays indicated that the acquired defect was due to an impairment of the production of plasminogen activator. The control group showed good reproducibility throughout the period of study.

The biologic significance of the fibrinolytic response to exercise and epinephrine remains as yet, unknown. It is postulated that it may represent, in part, the ability of the individual to generate circulating plasminogen activator to stress. Exercise and epinephrine also increases the coagulability of the blood and, on the basis of a dynamic equilibrium between coagulation and fibrinolysis, an increase in fibrinolysis would be anticipated. Iatridis and Ferguson[14] however observed that 11 of their 39 subjects failed to increase their circulating plasminogen activator following exhaustive exercise despite an apparent increase in coagulability. Burt group[16] concluded that the mean changes following strenuous exercise procedure were in favor of fibrinolysis, but examination of their results in more detail reveals that 2 of their 44 subjects gave a poor fibrinolytic response despite the fact that the coagulation changes were similar to those giving a marked fibrinolytic response.

The fact that hypercoagulability in association with increased fibrinolysis has been demonstrated during mental anxiety[26] as well as in exercise makes it possible to hypothesize that persons with an impaired mechanism for generating plasminogen activator may be subject to transient episodes of coagulation-fibrinolysis disequilibrium during their day-to-day living. This disequilibrium might arise either from an exaggerated increase in coagulation associated with a normal increase in fibrinolysis or vice versa. Should the extension of Astrup's hypothesis be substantiated, then these persons would be at risk to arteriosclerosis and/or thrombosis.

Evidence supporting this hypothesis is fragmentary. Cirrhotic patients are believed to have a low incidence of myocardial infarction[27] and it has been shown that they may possess an exaggerated fibrinolytic response to nicotinic acid[28] as well as a general tendency to hypocoagulability. There is also evidence that some patients with a proved history of myocardial infarction may show an abnormally high increase in the coagulation mechanisms following exercise.[11]

The role of mental stress in the etiology of arteriosclerosis and thrombosis is controversial: intimal trauma by repeated whiplash effects on unsupported parts of the arterial tree,[29] the mobilization of fat into the bloodstream and hypercoagulability[30] have all been prominent. Previous studies on the fibrinolytic enzyme system during University examinations failed to show consistent changes in the absolute resting levels of circulating plasminogen activator[31, 32] and this observation was confirmed in this study. However, the studies on the fibrinolytic responses studies would indicate that acute mental stress might be a situation in which coagulation fibrinolysis disequilibrium could arise in those subjects who were genetically poor fibrinolytic responders for this is a situation in which both the coagulation and fibrinolytic mechanisms are stimulated. Furthermore prolonged mental stress may produce a deleterious influence on a normally good fibrinolytic responder and it would appear that this effect can continue for some weeks beyond the crisis.

It is possible that concentrating our attention on the biologic significance of an individual's ability to generate plasminogen activator to stress in relation to the etiology of arteriosclerosis and focal thrombosis is either inappropriate and/or restricting. Wood and O'Meara[33] have postulated that the metastases of malignant tumors may be governed by the ability of the cancer cells to form and maintain a fibrin environment. Clifton[34] has reported that the induction of an active fibrinolytic state in animals given large intravenous doses of cancer cells, markedly reduced the number of metastases. The significance of this work remains as yet, unresolved but Thornes[35] has emphasized that an important factor in the spread of cancer may be the ability of the cancer cell to maintain its fibrin in the face of the opposing fibrinolysis of the host. Should this hypothesis be substantiated, then the ability of the host to generate plasminogen acti-

vator could be of some significance Furthermore, the work of Hardaway[27] and McKay[28] in studies on syndromes of disseminated intravascular coagulation suggest that an important factor in the recovery from these conditions would appear to be the ability of the individual to generate plasminogen activator Indeed, Hardaway has emphasized that situations of danger may arise, for instance in hemodynamic shock, if the endogenous fibrinolytic response is either too little or too late.

While it is recognized that these investigations have solved few of the problems outlined in the earlier paragraphs of this annotation, it is believed that the study of the fibrinolytic response of individuals represents a new approach to better understanding of the physiologic control mechanisms of the fibrinolytic enzyme system It is theoretically a more appropriate way of studying a system which is believed to be in a state of dynamic flux and has already revealed a defect in normal subjects which is not apparent from measurements of absolute resting levels. The biologic significance of this phenomenon, however must remain the subject of further studies.

J D Cash M.B B Sc., Ph.D M.R.C.P.E.
Blood Transfusion Service
Regional Blood Transfusion Centre
Royal Infirmary
Edinburgh 3 Scotland

REFERENCES

1 Rokitansky K. von. Über einige der wichtigsten Krankheiten der Arterien, Vienna, 1852 Meldinger
2. Virchow R. Gesammelte Abhandlungen zur wissenschaftlichen Medicin, Frankfurt, 1856, Staatsdruckerei
3 Duguid, J B. Thrombosis as a factor in the pathogenesis of coronary atherosclerosis, J Path. & Bact. 58:207 1946
4. Harrison, C. V Experimental pulmonary arteriosclerosis, J Path. & Bact. 60:289 1948.
5. Crawford, T and Levene C. I The incorporation of fibrin in the aortic intima, J Path. & Bact 64:523 1952.
6. Haust, M D Wyllie J C and More, R. H. Atherogenesis and plasma constituents, Am. J Path 44:255, 1964
7 Pickering, G. W Pathogenesis of myocardial and cerebral infarction nodular arteriosclerosis Brit. M J 1:517 1964.
8. Fearnley G. R. Fibrinolysis by adsorption, Nature 172:544, 1953
9 Sherry S., Fletcher A. P and Alkjaersig, N Fibrinolysis and fibrinolytic activity in man, Physiol. Rev 39:343 1959
10 Astrup, T The biological significance of fibrinolysis, Lancet 2:565 1956
11 Fearnley G. R Fibrinolysis London, 1965 Edward Arnold (Publisher) Ltd.
12. Fearnley G. R Balmforth, G and Fearnley E. Evidence of a diurnal fibrinolytic rhythm with a simple method of measuring natural fibrinolysis, Clin Sc 16:645 1957
13 Blix, S Studies on the fibrinolytic system in the euglobulin fraction of human plasma, Scandinav J Clin. & Lab. Invest. 13:Suppl. 58, 1961
14. Iatridis, S. G., and Ferguson, J H Effect of physical exercise on blood clotting and fibrinolysis, J Appl. Physiol. 18:337 1963
15. Ikkala, E., Myllyla, G., and Sarajas, H S. S. Haemostatic changes associated with exercise, Nature 199:459 1963.
16. Burt, J J Blyth, C. S., and Rierson, H. A. The effects of exercise on the coagulation fibrinolysis equilibrium, J Sport. Med. and Phys. Fitness (Torino) 4:213 1964
17 Biggs, R., Macfarlane, R. G., and Pilling J Observations on fibrinolysis, Lancet 1:402, 1947
18. Sawyer W D Fletcher A. P Alkjaersig, N and Sherry S.: Studies on the thrombolytic activity of human plasma, J Clin. Invest. 39:426, 1960.
19 Cash, J D Effect of moderate exercise on the fibrinolytic system in normal young men and women, Brit. M J 2:502, 1966.
20. Euler U S. von., and Hellner S Excretion of noradrenaline and adrenaline in muscular work, Acta physiol scandinav 26 183, 1952
21 Vendsalu, A. Studies on adrenaline and noradrenaline in human plasma, Acta physiol. scandinav 49 Suppl 173, 1960.
22. Genton, E Kern, F J and Von Kaulla, K. Fibrinolysis induced by pressor amines, Am. J Med. 31:564, 1961
23. Cash, J D and Allan, A G. E. The fibrinolytic response to moderate exercise and intravenous adrenaline in the same subjects, Brit. J Haematol. 13:376, 1967
24. Cash, J D and Woodfield, D G Studies on the fibrinolytic response to moderate, exhaustive, and prolonged exercise procedures in a group of normal subjects, Nature 215:628, 1967
25 Cash, J D and Allan, A. G. E. The effect of mental stress on the fibrinolytic reactivity to exercise, Brit. M. J 1:545, 1967
26. Ogston, D McDonald, G. A and Fullerton, H. W The influence of anxiety in tests of blood coagulability and fibrinolytic activity Lancet 2:521 1962.
27 Grant, W C., Wasserman, F Rodensky P L., and Thomson, R V The incidence of myocardial infarction in portal cirrhosis, Ann. Int. Med. 51 774, 1959
28. Fletcher A. P Biederman, O Moore, D Alkjaersig, N and Sherry S Abnormal plasminogen plasmin system activity in patients with hepatic cirrhosis Its cause and consequences, J Clin. Invest. 43:681 1964
29 Kaulla, K. N von and Kaulla, E. von Thrombin generation in normal subjects and cardiac patients, Circulation Res. 14:436, 1964.
30. Teson, M. A hemodynamic concept of atherosclerosis with particular reference to coronary occlusion, Arch Int Med 99:418, 1937
31 Friedman, M Rosenman, R. H., and Carroll, V Changes in serum cholesterol and blood clotting in men subjected to cyclic variation of occupational stress, Circulation 17:852, 1958.
32. Truelove S. C. The lability of human fibrinolysin, Clin. Sc 12 75 1953.

33. Wood S. P thogenesis of metastasis formation observed in vivo in the rabbit ear chamber Arch Path. 66:550, 1958
34. O Meara, R A Q Coagulative properties of cancers, Irish J M Sc. 391:474 1958.
35. Clifton E E Effect of fibrinolysin on spread of cancer Fed Proc 25:89 1966.
36. Thornes, R. D Host factors in neoplasia, Irish J M Sc 487:265 1966.
37. Hardaway R. M Syndromes of disseminated intravascular coagulation, Springfield Ill 1966, Charles C Thomas, Publisher
38. McKay D G. Disseminated intravascular coagulation, N w York 1965 P ul B Hoeber Inc. Medical Book Division, Harper & Row Publishers.

Micronodular phlebosclerosis

An aging change of the venules of the kidney and adrenal

I microscopic examination of the normal part of kidney with a large angiomyolipoma several dilated en les were observed with a peculiar fibromyomatous nod le of the wall protruding int th lumina hereinafter called micronodular phlebosclerosis A review of journals and text books [1-9] disclosed no description of such structure as either anatomic or a pathologic entity A total of 350 autopsies were reviewed divided into si age groups Microscopic examination of the hides of ll organs in 100 consecutive cases with er ge age of 62 years (range 41 t 87) revealed the presence of these tructures in 30 per cent of the kidney and 57 per cent of the adrenal glands but not in any other organ. Study of the six different age groups indicated that micronodular phlebosclerosis is not present t the time of birth nd t gradually increases n size nd number as ge ad ances. Microscopic tudies of 1 000 sections of 100 adrenal gland from 50 newborn nfant confirmed the absence of any similar structure t the tim of birth It appears from these tudies that micronod lar phlebosclerosis is frequently found in association with arteriosclerotic cardiovascula disease heumatic heart disease and malignant tumors. Histologically the nodules are formed by smooth muscle and/or fibrous tissue indicated by Gomori trichrome staining method. The kidney with micronod lar phlebosclerosis rev aled one or more dilated enules, mostly in the cortical region with a nodule protruding into the lum na. The nodules are well defined and easily visualized under low-power magnification At times they are of sufficient ize to obstruct the lumen partially or completely Occasionally the lesion is associated with more tha one enule and t times one enule present more than one micronodular phlebosclerotic wal le. I the adrenal glands the lesions were not only more frequent but also more prominent. It has been indicated in the literature[4,8] th t longitudinal muscle bundles i the wall of the eins of the adrenal gland by contraction control the hormonal output, but no indication of their absence at birth is made Thickening of the wall of these ven les in the adrenal medulla also has been elated to hypertension but in our series only 10 per cent of the cases had evidence of hypertension. Regardless of the immediate mechanism and histogenesis, micronodular phlebosclerosis appear to be an acquired, progressi e lesion which is seen more frequently with ad anced age.

Husheng M P yu M.D
Emil F Gubert M D
Department of Pathology
Clarksburg Veterans Administration Hospital W est Virginia University School of Medici e
Morgantown W Va.

REFERENCES

1 Warthi A. Old age The major involution, New York 1929 P l B Hoeber p. 199
2. Shock, N W Trends in gerontology ed 2 Palo Alto, Calif 1957 Stanford U iv Press, p 214
3. Stein A., Rosenblum, I and Leather R I timal sclerosis in huma veins, Arch. Path. 81:548 1966.
4 McMillan, G. C. I Abramson, D editor Blood vessels and lymphatics, New York, 1962, Academic Press, Inc. p 680.
5. Shock, N W Aging of the cardiovascular system, I Andrus, E., and Maxwell C., editors. The heart and circulation; research, Fed Am. Soc Exper Biol. 1:558, 1965
6. Lobstein, J F Traité de l'anatomie pathologique Paris, 1833, vol. 2 p. 555
7 H uswirth, L., and Eisenberg A.: Disseminated venofibrosis (phlebosclerosis) It clinical pathologic ign ficance Arch. P th. 11:857 1931
8. Lev M and Saphir O Arch. P th. 51 151 1951
9 Allen, A. The kidney ed. 2, New York, 1962, Grune & Stratton, Inc. p. 48.

10. Franklin, J. A monograph on veins, Baltimore, 1937, C. C. Sommers Company, p. 108.
11. Gore, I. J. Anderson, W. A. D. editor: Pathology, ed. 5, St. Louis, 1966, The C. V. Mosby Company, p. 597.
12. Saphir, O. A text on systemic pathology, New York, 1958, Grune & Stratton, Inc., p. 222.
13. Ham, A. Histology, ed. 3, Philadelphia, 1957, The Lippincott Company, p. 494.
14. Fergeson, J. The veins of the adrenal, Am. J. Anat. 5:63, 1906.
15. Symington, T. Morphology and secretory cytology of the human adrenal cortex, Brit. M. B. II. 18:117, 1962.
16. Goldzieher, M. and Sherman, I. Hypertrophy of muscles of suprarenal vein in hypertension, Arch. Path. 5:1, 1928.

Allergenic factors in penicillins and cephalosporins

Recent immunochemical research upon penicillins[1-8] and cephalosporins[9] has revealed in these antibiotics macromolecular residues which might account for some of the allergic and toxic reactions occasionally encountered in patients treated with these drugs. Techniques used for this purpose are essentially (1) fractionation of the antibiotics in concentrated solution by means of molecular sieves, dialysis, and precipitation, (2) immunization of guinea pigs and rabbits by the whole antibiotic and fractions or degradation products thereof, (3) skin tests with similar preparations in human subjects known to be hypersensitive to penicillins, and (4) therapeutic tests with antibiotics cleared of preformed residues.

All forms of penicillin are derivatives of 6-aminopenicillanic acid (6-APA) acylated at the amino group in the 6-position. This free amino group, corresponding to the α-amino group of cysteine, can form a covalent bond with carboxylic groups of other amino acids or peptides; the carboxyl group in the 3-position also forms linkages with ε-amino groups of amino acids, peptides, or proteins which can undoubtedly result up to a point the chemical processes employed in extraction. It is therefore not surprising to find that 6-APA, as prepared from natural penicillin G by addition of acylase-producing coliforms to deep vat cultures, contains even after standard B.P. or U.S.P. purification procedures residues of a proteinaceous substance. This can be separated by dialysing 6-APA to exhaustion, in which case the retentate dries as a fluffy cream-colored powder devoid of antibacterial activity or of β-lactam structure. Hydrolysis of this product in hot HCl under N yields a range of amino acids, indicating an origin from a protein or peptide much more complex than 6-APA, natural penicillins, or any complex formed by antibiotic molecules. This protein provokes the formation of specific γG and γM antibodies in guinea pigs and rabbits. Used for skin tests in six human subjects known to be hypersensitive to penicillins, the protein elicited wheal and flare reactions and, in one subject, anaphylaxis. Only two of these subjects reacted to 6-APA from which the protein had been removed by dialysis. There was therefore no doubt that a potent allergenic proteinaceous component was firmly bound to 6-APA prepared biosynthetically. The amino acid constitution of this component showed that it originated during biosynthesis and not by internal reaction or degradation of penicillin-like peptides. It had already been shown that 6-APA was immunogenic in experimental animals and cross-allergenic with penicillins irrespectively of side-chain, in hypersensitive human subjects.[4,5] Immediate allergic reactions, however, appear to be more closely linked to the protein complex, though the fact that this complex is strongly cross-reactive with penicillins but not with cephalosporins indicates that 6-APA or some product thereof is essential as a haptenic determinant, and further that the configuration of the sulfur ring is relatively more important than the lactam ring in this respect.

Similar macromolecular proteinaceous or peptide residues have now been identified by fractionation and immunochemical tests in several semisynthetic penicillins, and notably in ampicillin as well as in penicillin G. The yield varies, however, in different batches from the same or different makers. Ampicillin, one of the most reactive of the penicillins, with a free amino group available for direct peptide-bonding, usually yields a relatively large residue with several components as judged by chromatography. In the semisynthetic penicillins, as in 6-APA, the protein may be derived partly from the coliform enzyme used for deacylation, whereas in penicillin G it must be formed from peptides present in the fermentation liquor. Whatever its source—and it is likely that more than one set of biochemical precursors is involved—this protein must carry penicilloyl hapten to confer immunogenic specificity and allergenic cross-reactivity. The protein-complex from penicillin G is extremely potent, for when first tested it elicited strong cutaneous reactions in doses of 0.01 μg in two sensitized subjects, neither of whom reacted to 100 μg of the corresponding preparation, deproteinized by dialysis, and one of whom tolerated a therapeutic injection of 10 mg. intramuscularly. By analogy with other conjugates, 0.01 μg of the complex would correspond to 0.03 mμEq of penicilloyl groups. Subsequently to these investigations,

the writer has given deproteinized penicillin G to other hypersensitive subjects without adverse result. Knudsen and co-workers found that, out of 20 hypersensitive subjects who volunteered for tests, 11 reacted to standard but not to deproteinized penicillin G while 9 reacted to both preparations. Delayed reactions have however been encountered with deproteinized penicillin G. This is to be expected since it is known that penicillin G readily degrades in aqueous solution to benzylpenicillenic acid which forms stable conjugates with protein either by mixed disulfide linkages[?] or by amide linkage. Such conjugates are immunogenic with respectively penicillenic or penicilloic acid specificity and there is evidence[30] that these degradation products are involved as haptens in some allergic reactions. Even without degradation the benzylpenicillin molecule can undergo penicilloylation directly, in which case penicillin G will behave as hapten in delayed as in immediate responses. The best known form of penicilloylation is that which occurs at the carbonyl group of the opened lactam ring with the ε-amino group of lysine, a fact which has been used in the preparation of penicilloyl polylysine (PPL) as a reagent for skin tests.[31] A substantial proportion of patients with proved hypersensitivity to penicillin give positive reactions to intradermal tests with 1 to 5 mμEq of this substance, the exact proportion varies with the investigator and the number of lysine residues in relation to penicilloyl groups in the preparation. In the writer's experience with a preparation containing an average of 50 lysine residues per molecule used at 6×10 mEq of penicilloyl groups, positive skin reactions are obtained in about 50 per cent of subjects with verified reactions to therapeutic injections but some of these patients can in fact tolerate therapeutic injections given subsequently while some others, reacting negatively to PPL, react adversely to injections of penicillin G. In some subjects PPL is cross-reactive with the protein residues of penicillin G and 6-APA. In the absence of more precise data based upon an open surveillance—which is urgently needed and which is now being organized by the American Academy of Allergy—PPL must therefore be regarded as a reagent indicating that ε-type penicilloylation is involved in the allergy of a given patient and not as a complete screening agent for hypersensitivity to all forms of penicillin.

A further complication observed independently by the Beecham Research Group in England and by the writer in America, is that penicillins deproteinized by dialysis or gel-fractionation can undergo internal reactions leading to polymerization. The polymer formed by 6-APA is similar to, though probably smaller than the 7 or 8 unit peptide described by Grant and associates. This polymer is not immunogenic though it can elicit reactions in guinea pigs when used as a challenge for passive cutaneous anaphylaxis. With penicillin G polymerization may depend upon benzylpenicillenic acid substrates though with other penicillins and with cephalosporins, different chemical routes are involved leading with some of the derivatives, to polymers with strange colors and odors. If penicillins or cephalosporins are allowed to stand in concentrated solution at room temperature or even in the cold some of these products can be observed with the naked eye. It is unlikely that, in trace amounts, these polymers have any allergenic or toxigenic significance but their presence in larger amounts is obviously undesirable in therapeutic preparations, especially since they can form macromolecular complexes with the protein residues. It seems possible that some such complex formed in solution in multidose bottles which have been used for successive doses, might well act as a sensitizing antigen complete with adjuvant. Standard procedures for assaying, storing and administering the β-lactam antibiotics probably need reassessment in this regard.

With such varied immunochemical mechanisms at work, it is surprising that hypersensitivity to penicillins is not much more common than the accepted figure of 2 to 5 per cent. The explanation of this[32] probably resides in the power of the intact molecules or degradation products coupled as univalent haptens to neutralize the reactions by combining with antipenicilloyl antibody leading to what de Weck calls a "built-in inhibitor system" which could explain also some other immunologic paradoxes.

It is likely that the etiology of hypersensitivity to penicillins depends upon biologic and ecologic factors wider than the therapeutic use of the drugs. These other factors, which have been discussed more extensively elsewhere[33] include the prevalence of fungi capable of producing penicillin-like molecules, the use of the drug in animal feeding and veterinary practice, addition of crude antibiotics to milk to prevent bacterial decomposition—a practice by no means uncommon until recently in some dairy farming areas—and other ecologic considerations. Collectively these factors provide a variety of opportunities for low-grade sensitization to penicillin antigens, and it is not unreasonable to suppose that, in individuals thus affected, a few injections of therapeutic preparations can then convert the low-grade sensitization into the extraordinary hypersensitivity which is the unique feature of penicillin allergy. There are few if any antigens which can cause fatalities in microgram doses. The extremely high potency of the penicilloylated macromolecular residues fits this explanation. It remains to be seen if removal of these residues will lessen the problem. If so the usefulness and usage of penicillins will increase enormously, for there are few other contraindications.

The main clinical question arising from these new findings is whether penicillin purified by these new methods can be given with safety to patients with proved allergy. The answer to this is, unfortunately, uncertain until more clinical experience is on record. There are good grounds for believing that the sensitizing power of the deproteinized antibiotics will be substantially lower and there is evidence that some patients who are intolerant to the residues can in fact receive the deproteinized preparations without adverse reaction. The proof however can only come from more extensive usage and this will take time. Meanwhile if penicillin therapy is of life-saving importance—as in some forms of endocarditis and septicemia—there is

justification for trying the deproteinized preparations after preliminary skin tests with 100 μg and trial doses of 1 to 10 mg with resuscitative measures at hand.

G. T. Stewart, M.D.
Professor of Epidemiology and Pathology
Schools of Medicine and Public Health
University of North Carolina
Chapel Hill, N. C.

REFERENCES

1. Batchelor, F. R., Dewdney, J. M., Feinberg, J. G., and Weston, R. D.: A penicilloyl protein as a source of allergy to benzylpenicillin and 6-aminopenicillanic acid, Lancet 1: 1175, 1967.
2. Batchelor, F. R., Dewdney, J. M., and Gazzard, D.: Penicillin allergy: the formation of the penicilloyl determinant, Nature 206:362, 1965.
3. De Weck, A. L.: Some immunochemical properties of penicillenic acid, J. Exper. Med. 112: 1227, 1960.
4. De Weck, A. L.: Studies on penicillin hypersensitivity. I. The specificity of Rabbit antipenicillin antibodies, Internat. Arch. Allergy 21:20, 1962.
5. De Weck, A. L.: Personal communication, 1967.
6. Grant, N. H., Clark, D. E., and Alburn, H. E.: Poly-6-aminopenicillanic acid, J. Am. Chem. Soc. 84:876, 1962.
7. Knudsen, E. T., Robinson, O. P. W., Croydon, E. A. P., and Tees, E. C.: Cutaneous sensitivity to purified benzylpenicillin, Lancet 1: 1184, 1967.
8. Chisholm, D. R., English, A. R., and McLean, N. A.: Immunologic response of rabbits to 6-aminopenicillanic acid, J. Allergy 32:333, 1961.
9. Levine, B. B.: Studies on the mechanism of the formation of the penicillin antigens. I. Delayed allergic cross-reactions among penicillin G and its degradation products, J. Exper. Med. 112: 1131, 1960.
10. Levine, B. B.: Immunologic mechanisms of penicillin allergy, New England J. Med. 275: 115, 1966.
11. Parker, C. W., De Weck, A. L., Kern, M., and Eisen, H. N.: The preparation of some properties of penicillenic acid derivatives relevant to penicillin hypersensitivity, J. Exper. Med. 115:803, 1962.
12. Parker, C. W.: Penicillin allergy (editorial), Am. J. Med. 34: 747, 1963.
13. Stewart, G. T.: Cross allergenicity of penicillins, Lancet 1:509, 1962.
14. Stewart, G. T.: The penicillin group of drugs, Amsterdam, 1965, Elsevier Publishing Co.
15. Stewart, G. T.: Allergenic residues in penicillin, Lancet 1: 1177, 1967.
16. Stewart, G. T.: Biologic stability of cephalosporins, Proc. Internat. Cong. Chemotherapy, Vienna, June 23–July 1, 1967. In press.

Book reviews

DAS RUHE D BELASTUN ECG BEI SPORTLE N By I A Butschenko Leipzig 1967 (Johann Ambrosius Barth 248 pages

With the increasing interest in exercise and th let be monograph is timely The book consist of three parts, the first nd larger concerned with th bronic effects (training) on the resting ECG (Chapters I to III pp 7 t 86) the second part w th hanges d ring and after an exercise test (Chapters IV and V pp 87 t 109), and the last (nd smallest) w th 'bertra ung and beranstrengu g (Chapter VI pp 110 t 114) The oncept of excessiv work load (Uber mud g) is q t frequent in the German lit erature and therefore substantiation by ECG hanges would be of interest However the hanges described Chapter VI lack specifient

The sample of 1,250 athletes as listed in T ble 1 and 2 402 thletes as mentioned in the text is bstantial I nfort nat ly the results re presented crude distributions, terms of percentage of subjects n four arbitrary lasses for the variou ECG tems measured

For omparison with nt ained population the au hor used Vaquero sample (1947) collected Mexic City Serious objections can be ised the differences between the tw samples be due to differences of race geograph al h ion (Mexico C t is 8 000 feet altitude) nd different sex distribution as well as t different t ain ng ond tion As matter of fac the differences of some of the ECG tems bet een V quero Mexican sample and sedentary North American samples are the same direction as those lamed by he thor t be pk l for hron effect of training I iew of the lack of adequat sedentary ontrols, dr from he same population, the question of training effect on the resting ECG the author ma erial open t question

On he other hand the omparison of ECG hanges d ring nd after exhau tiv (graded) w rk on the bic le ergometer in 61 w ll trained and 91 not suff iently trained athletes is more adequat both in reg rd t sample selec tion nd st ist al ev luation (means nd S D) T ble 70 (p 96) gives detailed and interesting information on this series I is regrettable that new lead V as sed hich is similar t but not identical to, nd probably less sensit tha other oblique bipolar chest leads more commonly used in exercise tests. The extensiv list of references (pp 220 t 240) includes front Russian nd Ea tern Europea uthors hich is of considerable I terest. On the other hand references t recent nd importa t American investigations are incomplete

The book is profusel illu trated perhaps overillu trated In most ECG nly t me mark ing given There is den t tendenc to over interpretation of bnormality , th ECG hown as typical for an thlet ould be found among sedentary population attempt was made to obtain statisticall discriminatory values perhaps, this ma not be possible because the discrimination is probably poor

It is surprising that the author still adheres to the obsolete un pola theory of trietly local ized ECG patterns, as suggested by Goldberger n 1942

The book abound w th trong, but poorly supported convictions, for instanc on p 45 All these changes (lockwise rotation) greater R V tha R V (quit logical lockwise rotation) increase of R V nd S-V + R V prove the high f nctional capacity of the heart This I hard to reconcile with the incidence of 10 per cent low oltage ECG a I athletes in the a thor material In absenc of pathological onditions the low voltage is explained by the 'better developed skeletal musculat re (p. 68) 'The sim ltaneous depression of S-T nd P-Q below the isoelectric line fter t minute tanding-running in thletes must be considered as symptom of inadequat general bod dev lopment (Durchbild ng) (p 105) (Thi pattern is q te common in sinus tachycardia) How ever there are lso i terest ng result I ell trained thletes, the T-w v incre ses after maximum exertion, wh le it decreases in insuffi iently trained subjects. Of interest lso is the difference of the Q-T i terval-h art rat relationsh p t rest and during exercise (Fig 5 and 6)

The book can be recommended for those ho know the subject ll enough t separat inter esting new information from the body of the text.

PHYSIC L B SIS F C RCUL TORY TRANSPORT R GULATION) EXCH 4 Edited by I B Rees B M B Ch and Arthur C Guyton M D Phi delphia, London, 1967 W B. Saunders C mpa 381 pages Pric $20 00

This book ontains the papers presented t on ference held at the Colorado Medic l Center September 1966. The many papers are concerned with attempt t explain the physics of the function of the heart and irc lation through the use of models mathematics, hypothesis, implification, and assumption ll available experiment l data. The effort are good and the papers ery interesting The uthors present their idea ery well concerning th complex nature of the performance of the cardio ascular) tem. The particip t were mainly phy iologi t biophy i t engineers mathematicians patholog t nd even anatomist but there were no research cardiolog t or l icians eng ged i peripher l lar re-

search. Thus, as would be expected, the book should be of interest to investigators engaged in studies of hemodynamic phenomena and of little interest to clinicians except those involved in research who have a good background in physics and the fundamentals of cardiovascular physiology.

The discussions are good. By necessity the investigators were forced to deal with simplified models, theories, and assumptions. Nevertheless, their presentations are extremely interesting and should be of value not only to those actively engaged in such research, but to anyone who wishes to learn more about the physical aspects of the function of the cardiovascular system. Since the authors do not usually work with people or patients with heart disease or in fact do not appear to follow the clinical literature as reflected in the discussions and the bibliography, the papers are deficient in pathologic physiology. Nevertheless, those engaged in clinical research should also find this book valuable.

ADVANCES IN GERONTOLOGICAL RESEARCH, Vol. 2. Edited by Bernard L. Strehler. New York and London, 1967, Academic Press, Inc. 431 pages. Price $18.50.

Doctor Strehler has brought together in this volume several papers on gerontological research related to the aging process. The contributors are all from the United States of America and therefore represent little from other countries of the world. The subjects discussed are somatic mutations and the aging process, metabolism of ribonucleic acid in young and old rodents, regulation and deterioration of structure of membranes, cell and tissue culture in aging research, general immunology of aging, aging of ground substance in connective tissue biology and pathogenesis of vascular disease, and lipid peroxidation. All of these subjects are presented very well and the reader will find the papers most interesting. However, as would be expected, these studies do not yet even approach an answer to the pathogenesis of senescence but rather indicate some differences between old tissue and young or the structure in old and young animals. A good example is the discussion of vascular disease found in old people. The presentation really reviews the literature which has been done repeatedly at many other conferences and in papers on arteriosclerosis. Nevertheless, this is a very important book on an extremely important subject. The reader must realize that the subjects presented are only a few selected topics from authors in the United States of America and therefore do not include the interesting fundamental studies in progress in many other laboratories. This is a good book, however, for those interested in gerontology and in search of an answer to the problem of the aging process.

THE INNOCENT MURMUR. Edited by Cesar A. Caceres, M.D. and Lowell W. Perry, M.D. Boston, 1967, Little, Brown & Company. 288 pages. Price $13.50.

This book of 300 pages is concerned with one of the most important cardiac problems in clinical medicine. Drs. Caceres and Perry have done a very thorough job in this book. They have called upon 25 (23 physicians) well-qualified people to present them with the presentation of ideas and facts about innocent murmurs. The subject is clearly discussed in chapters devoted to history, sound production, auscultation, phonocardiography, definition, Still murmur, cardiorespiratory murmurs, venous hum, late systolic murmur, and other aspects. A large part of the book is in the form of a panel discussion with the contributors expressing their opinions about various aspects of the murmurs. This is a good book which should prove useful to all clinicians and students.

Announcement

The Third International Symposium on Drugs Affecting Lipid Metabolism will be held in Milan, Italy from Sept 9 to 11 1968 The joint Scientific Secretaries are Dr W. L. Holmes, The Lankenau Hospital Philadelphia, Pa. 19151 and Prof R. Paoletti Institute of Pharmacology of the University of Milan The sessions will be divided as follows Drugs affecting (1) FFA mobilization (2) Triglycerides (3) Cholesterol and bile acid metabolism (4) Serum lipoproteins (5) Tissue lipids and obesity (6) General For further information contact Miss H. J. Prain, Institute of Pharmacology University of Milan Via A. del Sarto 21 20129 Milan Italy

Postgraduate Course Pediatric Radiology Congenital Heart Disease will be held at Cornell University Medical College, Memorial Hospital Auditorium, 424 East 68th Street, New York City N. Y. from April 25 to 27 1968. Registration fee $75.00 Inquiries to: Herman Grossman M.D. Department of Radiology New York Hospital Cornell Medical Center 525 E. 68th St New York, N. Y. 10021

American Heart Journal

April 1968 Volume 75 Number 4

Editorial

Arrhythmias after myocardial infarction

Eric Stock M.B. M.R.A.C.P.
Melbourne Australia

It is now generally agreed that arrhythmias are very common in myocardial infarction but their significance is still under consideration

The reported incidence of monitored arrhythmias in myocardial infarction varies between 73 and 95 per cent.[1-4]

The recorded incidence of arrhythmias depends on a number of factors. It is higher with early admission of the patient following infarction with clinically severe infarctions, and with continuous monitoring

The writer has recently confirmed the high incidence of arrhythmias in a series of 200 continuously monitored infarctions, but found that major arrhythmias, i.e. defined as potentially serious, occurred in only 40 per cent of these patients.

Frequently two or more different types of arrhythmias occurred in the one patient defined as multiple, in contrast to the occurrence of a lone or solitary arrhythmia.

It is important to recognize that the incidence of major arrhythmias, and the proportion of multiple as against "lone arrhythmias, increase with the severity of infarction as judged by clinical hypotension cardiac decompensation and shock. Furthermore the incidence of multiple arrhythmias from below the atrioventricular (A-V) node increases with the severity of infarction

The over-all incidence of specific arrhythmias varies between 8.5 and 12.5 per cent.

Ventricular extrasystoles are present in a large proportion of cases, and both ventricular extrasystoles and sinus tachycardia are more commonly associated with severe infarction.

It is now generally accepted that the development of arrhythmias is associated with a high mortality rate There is considerable variation in the reported mortality rates associated with arrhythmias, namely between 42 and 60 per cent.[3,4,7] This variation is partly due to the inclusion of different types of arrhythmias in different series and partly depends on the continuity of monitoring In those series in which short transient episodes are recorded the incidence of arrhythmias is higher and therefore the mortality rates associated with arrhythmias become lower

We found that the over-all mortality rate of patients with arrhythmias was higher than that of patients without arrhythmias, and furthermore, found that patients with multiple" arrhythmias had a significantly higher mortality rate than those with "lone" arrhythmias. This was to be expected in view of the increasing

From the Cardiac Department, Royal Melbourne Hospital.
Received for publication Sept. 8, 1967

incidence of multiple arrhythmias in increasingly severe infarctions.

A comparison of the mortality rates of patients within the groups of mild severe and shock patients led to the important observation that in mild infarction arrhythmias, when treated do not cause an increased mortality rate and in cardiogenic shock the death rate is so extremely high that the occurrence of arrhythmias does not matter In the severe group the mortality rate associated with major arrhythmias is significantly higher than in patients without them[4]

Multiple infranodal arrhythmias, that is two or more consecutive arrhythmias such as ventricular tachycardia, ventricular fibrillation A V block or the conduction disturbance of complete bundle branch block when occurring in a patient with severe infarction, are almost uniformly fatal[4]

The prognosis associated with specific arrhythmias has previously been assessed without regard to the severity of infarction and the presence of other accompanying arrhythmias.[3,7,8]

When these are taken into account the following patterns become apparent. In severe infarction excluding cases with multiple infranodal arrhythmias, there appears to be no appreciable difference in the mortality rates between those arrhythmias arising above or below the A V node and those arising below the mortality rate remains high despite successful reversion.

Ventricular extrasystoles and sinus tachycardia when not associated with arrhythmias did not contrary to previous reports, adversely affect prognosis.

The increasing incidence of arrhythmias with increasing severity of infarction raises the question whether it was the severity of infarction or the arrhythmia itself which was responsible for the adverse effect on prognosis. The observation that a large number of patients die several days after the successful reversion of their arrhythmias[9] supports the contention that the arrhythmias may merely be symptomatic of severe infarction and that their control often delays rather than prevents death. The observation that multiple infranodal arrhythmias, which are uniformly fatal in severe infarction are not fatal in mild infarction,[4] supports this hypothesis. Further corroborating evidence is drawn from the fact that better oxygenation of patients, which reduces the incidence of arrhythmias, leaves the prognosis unaltered.[9]

The high mortality rate generally associated with arrhythmias had led to various forms of intensive treatment. However some arrhythmias revert spontaneously and many are not accompanied by hemodynamic complications.[9] If arrhythmias are merely symptomatic, the need to treat them specifically will depend on the presence of such complications.

The tachyarrhythmias cause decreased diastolic filling from shortening of the diastolic period This and the loss of effective atrial systole results in decreased systolic ejection and decreased coronary flow[9] In atrioventricular dissociation the loss of atrial systole is accompanied by a slow ventricular rate which may result in decreased cardiac output.[6] The magnitude of the above disturbances depends on the contractile force and the pathological state of the myocardium[10]

Major arrhythmias respond readily to treatment.[9] Electrical reversion is the treatment of choice for all tachyarrhythmias as it is the most effective and has the fewest side effects. Of the antiarrhythmic agents, lignocaine appears to be superior and preferable to propranolol and procaineamide, as the latter drugs often produce hypotension and myocardial depression[11] The prophylactic value of lignocaine is yet to be assessed. Bradycardias and first degree A V block respond to atropine,[9] and second and third degree A V block may respond to the additional use of isoproterenol and intravenous steroids. Opinions differ as to whether electrical pacing should be instituted before or after attempting control by medication only[12,13] The author prefers a trial of medical treatment before electrical pacing.

As the above therapeutic measures are effective and because arrhythmias with clinical complications can be detected by routine observation it may be argued that there is little to be gained from the detection of uncomplicated arrhythmias by the use of continuous monitoring

Some may imagine that the detection of all arrhythmias would be important in preventing major arrhythmias, and it is true that frequent atrial and ventricular extrasystoles often precede more serious atrial[14] and ventricular tachyarrhythmias while sinus bradycardia[15] and first degree A-V block often precede complete heart block. However the value of detecting such premonitory signs is offset by their high incidence without the development of serious arrhythmias, and also by the poor results of prophylactic antiarrhythmic treatment.[9] Oxygen administration by face mask appears to reduce the incidence of extrasystoles and major arrhythmias, and the prophylactic use of atropine may prevent heart block. Their routine use, plus the early correction of left ventricular failure by intravenous diuretics, may well reduce the incidence of all arrhythmias.

In the light of these findings, the value of routine monitoring needs to be reassessed critically Continuous monitoring and coronary care units were stimulated by the development of successful external cardiac resuscitation[1] and the electrical defibrillation of cardiac arrest.[17] "Sudden unexpected death occurs from ventricular fibrillation ventricular standstill, idioventricular rhythm and rupture of the ventricle. The latter two are almost invariably fatal but with ventricular fibrillation and ventricular standstill the response to resuscitative measures depends on the severity of infarction and on the delay between arrest and the institution of resuscitative measures. In cardiogenic shock and idioventricular rhythm resuscitation may temporarily restore effective circulation but patients usually fail to survive more than six weeks. Only with ventricular fibrillation does resuscitation lead to long term survival The long term results are excellent after resuscitation in mild infarctions, but in severe infarction the mortality rate remains high (60 per cent) despite successful reversion of fibrillation [18]

Effective resuscitation is thus confined to ventricular fibrillation. The incidence of ventricular fibrillation has been reported to be between 8 and 10 per cent but these figures are probably too high This may be partly due to the inclusion of cases of secondary fibrillation that is, ventricular fibrillation complicating resuscitation after other modes of cardiac arrest. With better patient care, the incidence of fibrillation in the first few days after infarction should be about 2 per cent,[9] and as the mortality rate following defibrillation is 50 per cent early resuscitation should result in a 1 per cent improvement of the over all prognosis.

Ultimately whether routine electrical monitoring will prove to be beneficial will depend on the comparative prognosis of monitored and unmonitored patients. Such comparisons are difficult because of the large number of variables affecting the prognosis of myocardial infarction [19] Meanwhile, the routine use of monitoring is indicated until such time that it can be shown that intensively treated unmonitored patients have the same prognosis as monitored ones.

REFERENCES

1 Imperial, E. S., Carballo, R., and Zimmermann, H. A. Disturbances of rate rhythm and conduction in acute myocardial infarction. A study of 153 cases, Am J Cardiol. 5:24 1960.

2. Spann, J F Moellering, R. C., J Haber E., and Wheeler E O Arrhythmias in acute myocardial infarction. A study using an electrocardiographic monitor for automatic detection and recording of arrhythmias, New England J Med. 271:427 1964.

3. Julian, D G., Valentine, P A., and Miller G. G. Disturbances of rate, rhythm, and conduction in acute myocardial infarction. A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring, Am J Med. 37:915, 1964

4. Robinson, J S., Sloman, G., and M Rae, C. Continuous electrocardiographic monitoring in the early stages of acute myocardial infarction, Med. J Australia 1:427 1964.

5 Meltzer L. E., and Kitchell, J B Arrhythmias and acute myocardial infarction, Prog Cardiovas. Dis 9:50, 1966

6. Stock, E., Goble, A., and Sloman, G. Assessment of arrhythmias in myocardial infarction, Brit. M J 2 719 1967

7 Rosenbaum, F F and Levine, S. A. Prognostic value of various clinical and electrocardiographic features of acut myocardial infarction. I. Immediate prognosis, Arch. Int. Med. 68:913, 1941

8 Askey J M and Neurath, O The prognostic significance of auricular fibrillation in association with myocardial infarction, Am. Heart J 29:575 1945

9 Stock, E. Assessment of continuous monitoring after myocardial infarction. I preparation.

15. Haden, R. F., Langefoen, P H., Rapoport, M I and McNerney J J The significance of sinus bradycardia in acute myocardial infarction, Dis. Chest 44:165, 1963.
16. Kouwenhoven, W B Jude, J R., and Knickerbocker: Closed-chest cardiac massage, J.A.M.A. 173:1064, 1960.
1 Lown, B., Neumann, J Amarasingham, R., and Berkovits, B. V Comparison of alternating current with direct electroshock across the closed chest, Am. J Cardiol. 10:233, 1962.
18. Stock, E. Assessment of management of cardiac resuscitation, Med. J Australia 1:545 1966.
19 Goble A. J Sloman, G and Robinson, J S. Mortality reduction in a coronary care unit, Brit. M J 1 1005, 1966.
20. Stock, E. Prognosis of myocardial infarction in a coronary care unit, Med. J Australia _:3 1967

Clinical communications

The effect of preoperative systemic blood pressure on closed mitral valvuloplasty

A study of 1,630 patients with up to 15 year follow-up

Herbert Benson, M.D.
Laurence B. Ellis, M.D.
Dwight E. Harken, M.D.
Boston, Mass.

In patients undergoing closed mitral valvuloplasty for mitral stenosis, the presence of preoperative mitral valve calcification and mitral insufficiency have an adverse influence upon prognosis. The importance of preoperative systemic hypertension, however, as a poor prognostic sign in such patients has not been generally recognized. Our recent experience suggested that hypertensive patients had a higher mortality than did others with similar degrees of mitral valve disease. Therefore, a review was carried out in a large group of patients who had undergone mitral valvuloplasty to determine the effect of hypertension upon operative mortality and late results.

Methodology

A review was made of 1,630 consecutive patients with predominant mitral stenosis who underwent closed mitral valvuloplasty between Sept. 26, 1951, and April 30, 1966. These 1,630 patients did not include the first 100 consecutive cases of the series previously reported because of the considerably higher operative mortality rate in this group. Fifty-two patients aged 60 or over at the time of operation were also excluded. Preoperative blood pressures were not available, largely due to misplacement of records, in 35 of these 1,630 patients, and the remaining 1,595 cases (97.8 per cent) formed the basis of this study. The patients were followed from 1 to 15 years postoperatively.

The preoperative blood pressures were taken almost exclusively from hospital records. The admitting hospital blood pressures recorded by a physician were used except in a very few instances when such were not available and the pressures from nurses' admitting notes or from preoperative office visits immediately preceding the operation were taken. The patients were divided into the three arbitrary categories of *normotensive* (less than 140 mm. Hg systolic *and* 90 mm. Hg diastolic), *borderline hypertensive* (either 140 to 159 mm. Hg systolic *or* 90 to 94 mm. Hg di-

From the Thorndike Memorial Laboratory, Second and [illegible] Harvard Medical Services, Boston City Hospital, The Surgical Service, Peter Bent Brigham Hospital, The [illegible] Surgical Service, Mount Auburn Hospital, Cambridge, Mass., and The Department [illegible] Medicine and Surgery, Harvard Medical School.
This study was supported in part by grants [illegible] HE 604 [illegible] from the National Heart Institute, National Institutes of Health, [illegible] Public Health Service.
Received for publication April 26, 1967.
Address: Heart Station, Boston City Hospital, [illegible] Avenue, Boston, Mass. 02118.

astolic) and *hypertensive* (over 159 systolic or 94 diastolic) The patients were further subdivided into two age groups less than age 40 (658 patients) and age 40 to 59 (937 patients)

All deaths during operation and after operation but before hospital discharge were classed as operative deaths. The follow up method has been previously described[2] The patients were contacted annually by questionnaires and their subjective postoperative status and their ability to carry out daily activities were assessed Records of complications and of the amount of cardiac therapy required were also obtained Furthermore, in many instances personal follow up examinations were carried out and physicians reports and hospital records were assessed Patients who were moderately or markedly better by improving one or more categories in the New York Heart Association Classification were classed as *improved* Patients were considered *unimproved* if they were slightly improved unchanged or worse

An analysis was made of the postoperative results at 5 and 10 years. Survival curves were calculated according to the method of Berkson and Gage In the calculation of the survival curves patients reoperated upon were dropped from the analysis as lost to follow up at the time of reoperation The validity of including or excluding patients reoperated upon in the survival calculations has been discussed previously[1] The slight discrepancy between the number of dead noted in the analysis at 5 and 10 years postoperatively and the number of dead noted by the survival curve analysis at the 5 and 10 year points was due to the difference in the statistical analytical methods employed The analysis at 5 and 10 years took into account only those patients who were operated upon at least 5 and 10 years ago whereas the survival curves embraced all patients regardless of the date of operation Also the patients reoperated upon were included in the 5 and 10 year results, but dropped from the survival curves.

In the 1,595 cases there were 90 operative deaths. Autopsies were obtained in 64 of these operative deaths (71 per cent) No attempt was made to assess autopsy data on those who died in the follow up period because of the paucity of autopsies in these patients and the fact that these autopsies were performed in different hospitals with different autopsy protocols.

Results

Prevalence of hypertension In the younger age group there were 24 hypertensive and 49 borderline hypertensive patients, representing only 3 7 and 4 per cent of the total respectively In the older age group, there were 100 hypertensive patients and 157 borderline hypertensive patients representing 10 7 and 16 7 per cent of the total respectively Combining both age groups there were 124 or 7.8 per cent hypertensive patients and 206 or 12 9 per cent borderline hypertensive patients (Table I)

Operative mortality rates In the younger age group the operative mortality rate

Table I Distribution of blood pressure

Blood pressure	Age < 40		Age 40-59		Totals	
	No.	Per cent	No.	Per cent	No.	Per cent
Normotensive patient	585	88 9	680	72 6	1 265	79 3
Borderline hypertensive patient †	49	7 4	157	16 7	206	12 9
Hypertensive patient ‡	24	3 7	100	10 7	124	7 8
Totals	658	100	937	100	1 595	100

*Less than 140 mm. Hg systolic and 90 mm. Hg diastolic.
†Either 140 to 159 mm. Hg systolic or 90 to 94 mm. Hg diastolic.
‡Greater than 159 mm. Hg systolic or 94 mm. Hg diastolic.

was markedly increased in the hypertensive and the borderline hypertensive patients when compared to the normotensive control patients. There was a 20.8 10.2 and 3 1 per cent mortality rate in the hypertensive borderline hypertensive and normotensive patients, respectively These differences were highly significant (p = 0 0001) In the older age group the operative mortality appeared less affected by the hypertension (Fig 1 Table II)

Status of survivors of operation at 5 years postoperatively A total of 536 patients in the younger and 673 in the older age group were followed 5 years. Patients who died in the interim or who were reoperated upon were included (Fig 2) The follow up was relatively complete in both age groups, only 19 patients, or 3.5 per cent, of the younger and 34 or 5 0 per cent, of the older age group were lost to follow up.

In the hypertensive patients less than 40 years old a lesser percentage were improved than among the normotensive and borderline hypertensive patients of the

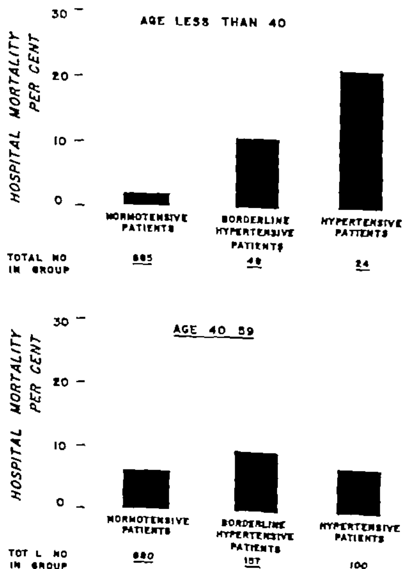


Fig 1 The relationship of preoperative systemic blood pressure to hospital mortality rate of patients under going mitral valvuloplasty.

Table 11 The relationship of hospital mortality rate to blood pressure

Age (years)	*Blood pressure*	*N*	*No. hospital deaths*	*Hospital mortality*
< 40	Normotensive patient	585	18	3.1
	Borderline hypertensive patient †	49	5	10.2
	Hypertensive patients‡	24	5	20.8
	Total	658	28	4.2
40–59	Normotensive patient	680	40	5.9
	Borderline hypertensive patients†	157	15	9.5
	Hypertensive patients‡	100	7	7.0
	Total	937	62	6.6
	Grand totals	1 595	90	5.6

*Less than 140 mm Hg systolic and 90 mm Hg diastolic.
†Either 40 to 159 mm Hg systolic or 90–94 mm Hg diastolic
‡Greater than 159 mm Hg systolic or 94 mm Hg diastolic

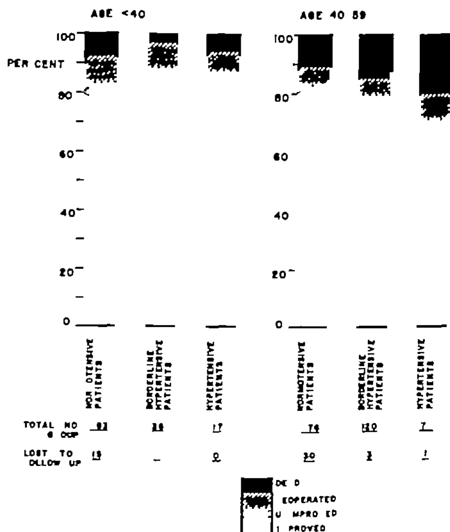


Fig 2 The relationship of preoper t y temic blood pressure t the stat of patient 5 y ars postoper tively

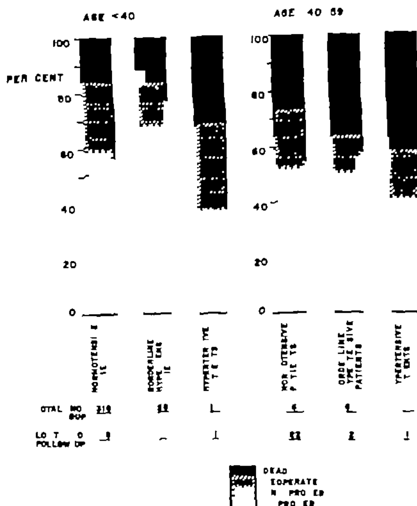


Fig 3 The relationship of preoperative systemic blood pressure to the status of patients 10 years postoperatively

same age group These differences were not statistically significant (Fig 2)

In the hypertensive patients of the 40 to 59 age group there was a lower percentage improved and a higher percentage of deaths, reoperations, and unimproved than in the normotensive and borderline hypertensive patients. These differences were statistically significant (p = 0 05) (Fig 2)

Status of survivors of operation 1 10 years postoperatively A total of 358 patients in the younger and 350 patients in the older age group were followed 10 years. Patients who died in the interim or who were reoperated upon were also included (Fig 3) In the younger age group 43 or 12 0 per cent and in the older age group 23 or 6 6 per cent were lost to follow-up

In the less than 40 age group, sizable and statistically significant differences appeared when normotensive and borderline hypertensive patients were compared to the hypertensive patients. The hypertensive patients had a lower percentage improved a higher percentage of reoperations and unimproved and a markedly higher percentage dead (p = 0 05) (Fig 3)

In the 40 to 59 age group a similar distribution was noted with the hypertensive patients having a lower percentage improved and a higher percentage dead than did the normotensive and borderline hypertensive patients. These differences, however were not statistically significant (Fig 3)

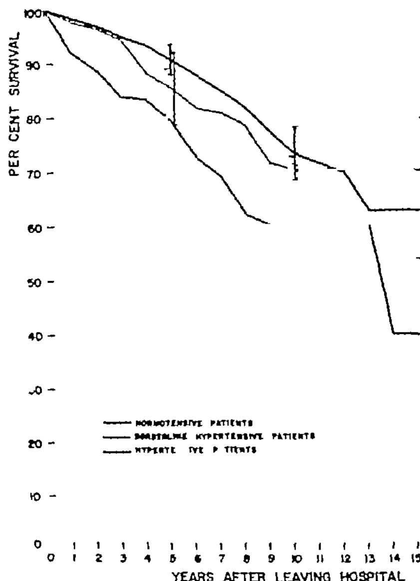


Fig. 4. The rel tionship of preoperativ sy temic blood pressure to the survival rates of p tients 40 to 59 years old undergoing mitr l valv loplasty. The ertical lines represent ±2 standard errors.

Survival Curves

There were too few patients with border line hypertension or with hypertension in the younger age group who survived the operation to calculate survival curves.

In the older age group the hypertensive patients had a lower per cent survival throughout all the 15 years of follow up (Fig. 4). Seventy nine per cent of the hy pertensive patients survived 5 years 60 per cent survived 10 years, and 40 per cent survived 15 years. In contrast 91 per cent of the normoten ive patients survived 5 years 4 per cent survived 10 years and 63 per cent survived 15 years. Borderline hypertensive patients up to 12 years follow up fared better than the hypertensive patients, but worse than the normotensive patients. From 12 to 15 years no deaths occurred in the borderl ne hypertensive group and their per cent survival exceeded that of the normoten ve group (Fig. 4).

Autopsy Data

No consistent relationship was observed in the 64 autopsy cases between incre sed blood pressure in either age group and the presence of macro- or microscopic renal

Table III Analysis of blood pressure in relation to renal infarction in 64 autopsied cases

Blood pressure	Renal infarction			No renal infarction			Total
	Age < 40	Age 40-59	Total	Age < 40	Age 40-59	Total	
Normotensive patients*	7	11	18	8	18	26	44
Borderline hypertensive patients†	1	7	8	1	1	2	10
Hypertensive patients‡	2	1	3	2	5	7	10
Totals	10	19	29	11	24	35	64

*Less than 140 mm. Hg systolic and 90 mm. Hg diastolic.
†Either 140 to 159 mm. Hg systolic or 90 to 94 mm. Hg diastolic.
‡Greater than 159 mm. Hg systolic or 94 mm. Hg diastolic.

Table IV Analysis of atrial fibrillation in relation to renal infarction in 64 autopsied cases

Rhythm	Renal infarction			No renal infarction			Total
	Age < 40	Age 40-59	Total	Age < 40	Age 40-59	Total	
Atrial fibrillation	6	18	24	7	20	27	51
Normal sinus rhythm	1	4	5	5	3	8	13
Totals	7	22	29	12	23	35	64

infarction nor was there any consistent relationship between the presence of atrial fibrillation and the presence of renal infarction (Tables III and IV).

Discussion

The major objectives of this study were to ascertain in a retrospective fashion whether elevations in blood pressure influence operative results and long-term follow-up of patients undergoing mitral valvuloplasty and also to review the literature concerning elevated blood pressure and mitral stenosis. The admitting hospital blood pressure was used to divide arbitrarily the patients into three categories of blood pressure. It is recognized that there are objections to the use of a single preoperative hospital blood pressure taken by different observers for analysis. Anxiety of a patient before an operation, anxiety of a patient in a hospital, and observer variation may all produce spurious elevations or errors in blood pressure determination. Some objective support for the validity of the elevated blood pressures in this series was gained by relating nephrosclerosis at autopsy to the level of preoperative blood pressure (Table V). The presence or absence of nephrosclerosis was noted in 60 of the 64 autopsied cases. In the normotensive patients there were fewer patients with nephrosclerosis than without nephrosclerosis. In the hypertensive patients, there were more patients with nephrosclerosis. These differences were statistically significant ($p = 0.05$).

There have been conflicting reports concerning the prevalence of hypertension in mitral stenosis. Gibson in 1909 and subsequently others[2-7] claimed that the prevalence of hypertension in mitral stenosis exceeded that in normal controls. Others found little difference in blood

Table V. The relationship of nephrosclerosis to blood pressure

Blood pressure	Nephrosclerosis			No nephrosclerosis			Total
	Age < 40	Age 40-59	Total	Age < 40	Age 40-59	Total	
Normotensive patients*	3	11	14	9	18	27	41
Borderline hypertensive patients†	1	4	5	1	4	5	10
Hypertensive patients‡	2	5	7	1	1	2	9
Totals	6	20	26	11	23	34	60

*Less than 140 mm. Hg systolic and 90 mm. Hg diastolic.
†Either 140 to 159 mm. Hg systolic or 90 to 94 mm. Hg diastolic.
‡Greater than 159 mm. Hg systolic or 94 mm. Hg diastolic.

pressure between patients with mitral stenosis and controls. Evidence has also been presented that hypertension is relatively uncommon in mitral stenosis.[13,14] The data from the various series are difficult to compare because of various definitions of hypertension, of inadequate controls in several instances, and of the great span of more than 50 years over which the different studies were conducted.

Our data do not clarify these discrepant opinions concerning the prevalence of hypertension in mitral stenosis. Since our analysis was confined to patients with mitral stenosis requiring operation, it dealt only with a selected population of patients and was not necessarily representative of the entire population of patients with mitral stenosis.

It was noted by Keith and associates[15] in 1963 in their series of 94 patients, that systemic blood pressure was greater than 140/90 in 6 patients. The outcome of mitral valvuloplasty in these 6 patients was not good since 3 patients died at operation, 2 had poor results, and only 1 had a good result. Our data indicates that in younger patients an elevation in blood pressure carries a markedly increased risk of operative mortality. In the older age group this added risk is not evident.

In a study of 389 patients followed 5 to 12 years following mitral commissurotomy, Galloreto and Tardif[1] found that preoperative arterial hypertension (the levels were not defined) occurred in 1 per cent of those with excellent results, in 0.5 per cent of those with good results, and 3 per cent of those with fair results. To our knowledge there are no other studies commenting upon the effect of hypertension on the postoperative prognosis of mitral commissurotomy.

Our data indicate that preoperative hypertension as defined has a definite adverse effect on the postoperative course of patients undergoing mitral valvuloplasty. Hypertensive patients had in general a higher percentage mortality and lower percentage of sustained improvement than did normotensive and borderline hypertensive patients at 5 and 10 years postoperatively. These differences, although not consistently statistically significant, were such as to suggest an adverse effect of hypertension.

The survival curves further strengthen the prospect of an adverse prognosis with preoperative hypertension. In follow-up studies up to 12 years, the per cent survival was consistently less in hypertensive patients when compared to the normotensive controls. The borderline hypertensive patients were between these two extremes. It may be argued that the survival curve of the hypertensive patients reflects the older age of such patients and not an adverse effect of hypertension. The survival curves were calculated in an age group encompassing 19 years (ages 40 to 59). Because of this 19 year age spread it is conceivable that there was a large number of hypertensive cases who were relatively old (55 to 59) and a small number who were

relatively young (40 to 44) However the number of cases of hypertension was evenly distributed with regard to age Furthermore, the number of cases of borderline hypertension was also evenly distributed There was however an uneven distribution of the normotensive group with a relatively large number of younger cases. To what extent this influenced the normotensive survival curve when compared to the other two is not known There remains, however a large difference in per cent survival between the borderline hypertensive patients and the hypertensive patients which supports the concept of an adverse effect of hypertension

Our data do not support previous findings of an association of hypertension and renal infarction nor of an association of atrial fibrillation and renal infarction As noted by others [12] we also found a high degree of association between hypertension and atrial fibrillation in both age groups ($p = 0.0007$ and $p = 0.0003$) This however does not prove a causal relationship between atrial fibrillation and hypertension. The meaning of this association is unclear

We found a highly significant relationship between increased cardiac limitation and hypertension in the older age group ($p = 0.0001$) and it could be argued that the hypertension was, in part secondary to large numbers of patients with congestive heart failure and its attendant increased peripheral resistance in this category Increased peripheral resistance may well be a factor contributing to the presence of hypertension in some cases, but congestive heart failure often leads to decreased blood pressure in spite of this increased peripheral resistance Furthermore it could be speculated that hypertension is a primary factor causing increased cardiac limitation

We therefore may only hypothesize on the pathogenesis of hypertension in mitral stenosis. Although in some cases it may be due to renal embolization secondary to atrial fibrillation our data do not support such a consistent over all causal relationship. It may also be due in some instances to the presence of congestive heart failure and its secondary increased peripheral resistance. On the other hand it may be completely independent of the associated mitral valve disease

It has been widely believed that hypertension improves the prognosis in unoperated mitral stenosis The hypertension was thought to lead to left ventricular dilatation that in turn would stretch the atrioventricular ring and open the stenotic mitral orifice Another rationale offered for this hypothetical advantage of hypertension was that there was right ventricular overload in mitral stenosis leading to an imbalance of the two ventricles. By imposing a load on the left ventricle with hypertension this imbalance was corrected [7] Alternatively others found no appreciable change in the life expectancy in the presence of mitral stenosis unoperated upon when the hypertensive patients were compared to normotensive patients[11] while still others found that hypertension in mitral stenosis without operation was a bad prognostic sign.[12]

The pathogenetic mechanism of the adverse effect of preoperative hypertension in mitral stenosis is also unclear It may be that in hypertensive patients otherwise mild degrees of mitral insufficiency following valvuloplasty become more pronounced because of increased left ventricular pressures. Alternatively this adverse effect may be due to the volume overloading after the relief of mitral stenosis of a left ventricle already working against increased pressure It may also be argued that there is a general nonspecific adverse effect of hypertension on patients undergoing any surgery and that our series reflects this general adverse effect This latter possibility may indeed be valid but it cannot be verified in this present study

It has been well established that the presence of preoperative findings such as mitral insufficiency and mitral valve calcification have an adverse influence upon the prognosis following mitral valvuloplasty The presence of preoperative hypertension is another such adverse factor and should also be considered when selecting patients for closed mitral valvuloplasty

Summary

A total of 1 630 consecutive patients with predominant mitral stenosis who under

went closed mitral valvuloplasty have been reviewed. Preoperative blood pressures were used to classify the patients into three categories: normotensive, borderline hypertensive, and hypertensive patients. In terms of operative mortality rate, late improvement, reoperations, and survival, preoperative hypertension in general carried a poor prognosis. No meaningful association between the presence of hypertension and postmortem renal infarction or between the presence of atrial fibrillation and postmortem renal infarction could be found. It was felt that preoperative hypertension should be considered as another, hitherto largely unrecognized, adverse prognostic factor in selecting patients for mitral valvuloplasty.

We are indebted to Dr. Hugo Muench of the Department of Bio-Statistics, Lemuel Shattuck Hospital, Jamaica Plain, Mass., for his aid with the statistical aspect of this material.

REFERENCES

1. Ellis, L. B., and Harken, D. E.: Closed valvuloplasty for mitral stenosis. A twelve-year follow-up study of 1571 patients, New England J. Med. 270:643, 1964.
2. Ellis, L. B., Harken, D. E., and Black, H.: A clinical study of 1,000 consecutive cases of mitral stenosis two to nine years after mitral valvuloplasty, Circulation 19:803, 1959.
3. Berkson, J., and Gage, R. P.: Calculation of survival rates for cancer, Proc. Staff Meet. M Clin. 25:270, 1950.
4. Gibson, G. A.: Diseases of the mitral valve, Allbutt: System of medicine, London, 1909, Macmillan and Co., vol. 6, p. 360.
5. Cowan, J., and Fleming, G. B.: The association between mitral stenosis and renal fibrosis, Quart. J. Med. 5:309, 1912.
6. Boas, E. P., and Fineberg, M. H.: Hypertension in its relationship to mitral stenosis and aortic insufficiency, Am. J. M. Sc., 172:648, 1926.
7. Levine, S. A., and Fulton, M. N.: The relation of hypertension to mitral stenosis, Am. J. M. Sc. 176:465, 1928.
8. Obeyesekere, H. I., Dulake, M., Demerdash, H., and Hollister, R.: Systemic hypertension and mitral valve disease, Brit. M. J. 5439:441, 1965.
9. Horns, H. L.: Association of hypertension and mitral stenosis, Am. Heart J. 28:433, 1944.
10. Roseman, M. D., and Wasserman, F.: The incidence of hypertension in mitral stenosis, New England J. Med. 245:450, 1951.
11. Gray, I. R.: Mitral stenosis and hypertension, Brit. Heart J. 16:165, 1954.
12. Brumm, H. J., and Smith, H. L.: Hypertension associated with mitral stenosis. Report of forty four cases, Minnesota Med. 24:664, 1941.
13. Wood, P. H.: Diseases of the heart and circulation, London, 1956, Eyre and Spottiswoode, p. 547.
14. Bechgaard, P.: Arterial hypertension. A follow-up study of one thousand hypertonics, Acta med. scandinav. 126, Suppl. 172, 1946.
15. Keith, T. A., Fowler, N. O., Helmsworth, J. A., and Gralnick, H.: The course of surgically modified mitral stenosis. A study of 94 patients with emphasis on the problem of restenosis, Am. J. Med. 34:308, 1963.
16. Gualtoreto, O., and Tardif, B.: Observations on the value of mitral commissurotomy. An analysis of long-term results, Canad. M. A. J. 89:589, 1963.
17. Gronath, A.: Mitral valvuloplasty. A clinical and hemodynamic pre- and postoperative study, Acta med. scandinav. 178, Suppl. 433, 1965.

The corrected orthogonal electrocardiogram in normal children

McFee and Parungao lead system

Raúl Gamboa, M.D.
*Nancy White, M.D.***
Dallas, Texas

The wide scatter of normal ranges for electrocardiographic parameters in children represents a major obstacle to correct interpretation of ECG's for the pediatric patient. The intra- and inter-individual variability of the lead fields of the conventional 12 lead ECG[1-3] probably contributes significantly to the broad distribution of normal values. The development of corrected orthogonal lead systems which exhibit more constant lead fields, regardless of variations in body build, facilitates a better quantitative approach to electrocardiographic interpretation. Several studies done in adults seem to demonstrate that much of the clinical information contained in the standard 12 lead ECG may be furnished by the corrected orthogonal 3-lead systems.[4-6] These studies suggest that application of the corrected lead systems to pediatric electrocardiography might reduce the wide range of normal findings, and consequently lead to a better separation of normal from abnormal readings.

Of the orthogonal lead systems which have been proposed, it would appear that those based on multiple electrode networks present certain theoretical advantages.[7] Among these systems, the one proposed by McFee and Parungao represents a careful compromise between the simultaneous needs to maximize accuracy and to minimize complexity. Recently Brody and Arzbaecher[9] have shown that in the homogeneous model, the "axial" lead system of McFee and Parungao is superior to the lead systems of Frank[1] and of Schmitt and Simonson. In addition Duchosal and Pasche[11] have recently emphasized the greater reliability of the axial lead system for routine clinical use.

The present study was undertaken in order to define the normal characteristics of the child's orthogonal ECG as obtained by means of McFee and Parungao's lead system.

Material and methods

Orthogonal ECG's (X, Y and Z leads) were taken from 100 normal children aged 1 to 15 years, who were considered free from any cardiovascular abnormality on the basis of history and physical examination, and in some cases, standard electrocardiography and chest x-ray. Fifty per

From the University of Texas Southwestern Medical School Department of Pediatrics.
Supported in part by the Texas Heart Association and the Dallas Heart Association.
Received for publication April 27, 1967.
*This work was done during the tenure of an Advanced Research Fellowship from the American Heart Association.
**Fellow in Pediatric Cardiology, Texas State Department of Health, Crippled Children Division, in cooperation with the Children's Bureau.

went closed mitral valvuloplasty have been reviewed Preoperative blood pressures were used to classify the patients into three categories normotensive border line hypertensive, and hypertensive patients. In terms of operative mortality rate late improvement reoperations, and survival preoperative hypertension in general carried a poor prognosis. No meaningful association between the presence of hypertension and postmortem renal infarction or between the presence of atrial fibrillation and postmortem renal infarction could be found It was felt that preoperative hypertension should be considered as another hitherto largely un recognized adverse prognostic factor in selecting patients for mitral valvuloplasty

We are indebted t Dr Hugo Muench of the Department of Bio-St tistics, Lemuel Shattuck Hospital, Jamaica Plain Mass for his aid w th the statistical aspect of this material.

REFERENCES

1 Ellis, L B nd Harken, D E Closed valvuloplasty for mitral stenosis. A tw lve-year follow up study of 1571 patients, New England J Med 270:643 1964
2 Ellis, L B Harken, D E, and Black, H A linic l tudy of 1 000 consecutive cases of m tral t nosis tw t me years after mitral valvuloplasty Circulation 19:803 1959
3 Berkson, J and Gage, R P Calculation of survival rates for cancer Proc Staff Meet Mayo Clin 25:270, 1950
4 Gibson, G. A Diseases of the mitral al Allbutt Sy tem of medicine, London, 1909 Macmillan and C vol 6 p 360.
5 Cowan, J and Fleming G B. The association between mitral tenosis and renal fibrosis, Quart. J Med. 5:309 1912
6. Boas, E. P and Fineberg, M H: Hypertension in its relationship to mitral tenosis and aortic insufficiency Am. J M Sc., 172:648, 1926.
7 Levine, S A. and Fulton, M N The relation of hypertension to mitral stenosis, Am. J M Sc. 176:465, 1928.
8 Obeyesekere, H I Dulake M Dewerdack, H and Hollister R. Sy temic hypertension nd mitral valve disease, Brit. M J 5459:441 1965.
9 Horns, H L. Association of hypertension and mitral stenosis, Am. Heart J 28:435 1944
10. Roseman, M D and Wasserman, F The incidence of hypertension i mitral stenosis, New England J Med. 245:450, 1951
11 Gray I R. Mitral stenosis nd hypertension, Brit. Heart J 16 165 1954
12. Brumm, H J and Smith, H L. Hypertension associated with mitral stenosis. Report of forty four cases, Minnesota Med. 24:664 1941
13. Wood, P H Diseases of the heart and circulation, London, 1956, Eyre and Spottiswoode p. 547
14. Bechgaard, P Arterial hypertension. A follow up study of one thousand hypertonics, Acta med scandinav 126 Suppl. 172, 1946.
15 Keith, T A. Fowler N O Helmsworth, J A., and Gral ick, H The course of surgically modified mitral stenosis. A study of 94 patients w th emphasis on the problem of restenosis Am. J Med. 34:308, 1963.
16. Giallorreto, O and Tardif B. Observations on the value of mitral commissurotomy: An analysis of long-term results, Canad M.A.J 89:589 1963.
17 Gronath A. Mitral valvuloplasty A clinical nd hemodynamic pre- and postoperative study Acta med. scandinav 178 Suppl. 433, 1965

Table I. QRS interval and age

	Total group	Age groups (yrs.) 1-4	5-10	11-15
QRS interval (sec.)				
Mean ± S.D.	0.070 ± 0.006	0.065 ± 0.005	0.070 ± 0.006	0.075 ± 0.007
Range	0.055 → 0.085	0.055 → 0.080	0.065 → 0.085	0.065 → 0.085
		1-4 vs. 5-10: $p > 0.05$; 1-4 vs. 11-15: $p < 0.05$	5-10 vs. 11-15: $p > 0.05$	

Limits of 96-percentile range.

Table II. Measurements of QRS in scalar leads X, Y, and Z

	X	Y	Z
Q magnitude (mv.)			
Mean ± S.D.	0.21 ± 0.07	0.17 ± 0.09	0.95 ± 0.41
Range	0.04 → 0.53	0.04 → 0.40	0.13 → 1.87
Q duration (sec.)			
Mean ± S.D.	0.011 ± 0.008	0.015 ± 0.010	0.039 ± 0.012
Range	0.005 → 0.045	0.005 → 0.0[illegible]3	0.015 → 0.040
R magnitude (mv.)			
Mean ± S.D.	1.60 ± 0.42	1.61 ± 0.46	1.43 ± 0.37
Range	0.63 2.5	0.63 → 2.70	0.60 → 36
R duration (sec.)			
Mean ± S.D.	0.047 ± 0.020	0.033 ± 0.006	0.043 ± 0.057
Range*	0.017 0.073	0.025 0.050	0.0[illegible]2 → 0.050
S magnitude (mv.)			
Mean ± S.D.	0.50 ± 0.30	0.33 ± 0.20	
Range	0.12 1.81	0.08 → 0.70	
S duration (sec.)			
Mean ± S.D.	0.015 ± 0.011	0.012 ± 0.011	
Range	0.007 0.035	0.005 → 0.035	
Q/R magnitude (ratio)			
Mean ± S.D.	0.11 ± 0.06	0.05 ± 0.05	0.72 ± 0.33
Range	0.03 → 0.25	0.03 → 0.1	0.09 1.0
R/S magnitude (ratio)			
Mean ± S.D.	4.82 ± 3.47	6.78 ± 5.10	
Range	0.77 → 15.50	1.66 → [illegible].47	

*Limits of 96-percentile range.

with the Q/R ratio). Fig. 3 shows the plotting of the Q/R ratio of the Z lead against age. It may be seen that ratios greater than 1 are observed only below 5 years of age. Fig. 4 shows the scalar X, Y, and Z leads, constructed from the mean values of Q, R, and S, and the amplitude ratios, arranged according to age groups.

Table III presents the quantitative analysis of early and late QRS vectors of X, Y, and Z leads taken at 0.01 second intervals, their spatial magnitudes, and their spatial orientations in terms of azimuth and elevation.

Table IV shows the normalized data of the QRS complex, including scalar amplitude, spatial magnitude and orientation, spatial velocity, and the maximum spatial

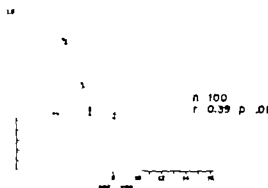


Fig. 3. The Q/R ratio of the Z lead plotted against age.

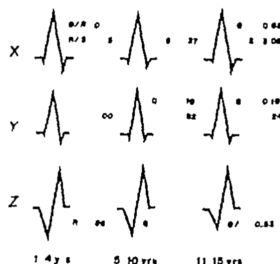


Fig. 4. Scalar X, Y, and Z leads constructed from the mean values of Q, R, and S deflections. The leads and corresponding amplitude ratios are arranged according to age groups.

magnitude (MSM). Fig. 5 shows the mean values of the curves of spatial magnitude, orientation, and velocity, and the 96-percentile ranges. As disclosed in Table IV and Fig. 5, initial QRS vectors are oriented anteriorly and slightly superiorly with spatial magnitude and velocity at the level of 0.58 and 0.8 mv. per millisecond, respectively. The maximum mean spatial magnitude, 2.05 mv., is reached between the 3/8 and 4/8 interval of the QRS. At this time, the spatial velocity approaches maximal value of 0.22 mv. per millisecond and the curves of spatial orientation show posterior (320°) and inferior (35°) orientation. The final vectors are directed toward the right, posteriorly and superiorly, and present smaller values for the spatial magnitude and velocity, 0.03 and 0.01 mv. per millisecond, respectively.

The possible influences of such variables as age, body weight, body surface area, and chest circumference on the maximum spatial magnitude of the QRS complex were analyzed statistically (Table V). The mean maximum spatial magnitude is similar for all the groups. Comparisons of all individual values by analysis of variance for a complete randomized design model[13] demonstrated no significant differences among them.

Discussion

QRS duration. Although the present study does not demonstrate a highly significant relationship between age and QRS duration, it is possible to observe a partial association indicating a longer QRS duration in the older children. Furthermore, noticeable differences are observed when comparing our data, particularly for the first two age groups (0.065 sec. mean for 1 to 4, and 0.070 sec. mean for 5 to 10 years of age) with the values reported by Draper and associates[14] for adults (0.093 sec. mean). It is conceivable that the differences between children and adults might be related to the growth of the heart. It has been shown by Linzbach[15] that during physiologic growth, the myocardial fibers enlarge. If the ventricular mass is increased, the QRS must increase in duration because the activation wave will take longer to course through the ventricles. It is noteworthy that, although there is a fifteenfold increase in heart weight from birth to adulthood,[4] the QRS duration increases steadily but never exceeds twice its value at birth. This can be explained, as suggested by Lepeschkin,[17] by simultaneous increase in conduction rate due to the growth in diameter of the conduction fibers. Hecht[18] has shown that the differences in conduction velocity in normal cardiac tissues depend largely upon the fiber diameter.

Although no comparable data on the duration of the QRS waves of the orthogonal electrocardiogram in infants and children have been published, it is interest

Table III *Quantitative analysis of early and late QRS vector*

Time (sec.)	Scalar amplitude (mv.) X	Scalar amplitude (mv.) Y	Scalar amplitude (mv.) Z	Spatial magnitude (mv.)	Spatial orientation (degrees) Azimuth	Spatial orientation (degrees) Elevation
0.01 after QRS onset						
Mean ± S.D	−0.06 ± 0.13	−0.04 ± 0.12	−0.45 ± 0.20	0.90 ± 0.24	90 ± 20	+5 ± 15
Range	−0.60 → 0.58	−0.30 → 0.20	0.00 → 1.20	0.15 → 1.40	18 → 140	−40 → +55
0.02 after QRS onset						
Mean ± S.D	0.48 ± 0.30	0.30 ± 0.37	−0.80 ± 0.50	1.18 ± 0.39	50 ± 29	+20 ± 15
Range	−0.07 → 1.25	−0.18 → 1.34	−1.75 → 1.15	0.45 → 2.39	87 → 150	−40 → +30
0.03 after QRS onset						
Mean ± S.D	1.20 ± 0.50	1.15 ± 0.39	0.17 ± 0.68	2.00 ± 0.50	330 ± 25	+40 ± 12
Range	0.14 → 2.50	0.10 → 2.40	−0.85 → 1.75	1.10 → 3.00	300 → 35	+10 → +30
0.04 after QRS onset						
Mean ± S.D	0.50 ± 0.70	0.68 ± 0.60	1.10 ± 0.50	1.70 ± 0.45	280 ± 30	+25 ± 20
Range	−0.78 → 2.00	−0.80 → 2.00	0.00 → 2.00	0.75 → 2.50	260 → 10	+29 → −10
0.01 before end of QRS						
Mean ± S.D	0.01 ± 0.03	−0.02 ± 0.02	0.03 ± 0.05	0.02 ± 0.05	220 ± 70	−15 ± 12
Range	−0.07 → 0.04	−0.07 → 0.00	0.00 → 0.09	0.00 → 0.30	200 → 260	0 → −25
0.02 before end of QRS						
Mean ± S.D	−0.07 ± 0.05	−0.04 ± 0.07	0.04 ± 0.08	0.06 ± 0.10	240 ± 30	−12 ± 18
Range	−0.38 → 0.06	−0.35 → 0.10	0.00 → 0.40	0.00 → 0.58	170 → 340	−25 → +30
0.03 before end of QRS						
Mean ± S.D	−0.09 ± 0.15	−0.06 ± 0.12	0.28 ± 0.25	0.35 ± 0.30	250 ± 15	+5 ± 20
Range	−1.10 → 0.18	−0.60 → 0.10	0.00 → 1.25	0.00 → 1.45	210 → 300	+30 → −25
0.04 before end of QRS						
Mean ± S.D	−0.21 ± 0.28	−0.05 ± 0.30	0.80 ± 0.29	1.00 ± 0.39	240 ± 13	+5 ± 15
Range	−1.25 → 0.40	−0.15 → 1.00	0.10 → 1.70	0.20 → 2.00	225 → 300	−30 → +30

*Limits of 96-percentile range.

ing to compare these measurements with those obtained from adult subjects. As shown in Table II all the values are lower than those observed in adults, except the duration of the Q wave in Lead Z which shows a mean of 0.039 sec. as compared with 0.033 sec reported by Draper and associates.

QRS magnitude and orientation. Comparison of our data with measurements in adults reported by Tannenbaum and coworkers, who used McFee and Parungao's lead system demonstrates higher values for every deflection of the QRS complex in children. The significance of these differences remains to be evaluated. The study of the amplitudes of the three waves of the QRS complex reveals that the Q wave of Lead Z is the only deflection which is related to age, body surface and body weight. Similarly the Q/R ratio in the Z lead is the only amplitude ratio significantly associated with these parameters. The variation of the Q/R ratio in Lead Z probably reflects the progressive changes in the anatomic relationship between the right and left ventricles that are associated with growth.[20] The importance of quantitatively defining this evolutionary pattern lies in its application to the diagnosis of ventricular hypertrophy in infants and children.

It has been shown by Yano and Pipberger[21] that the analysis of instantaneous spatial vectors, in terms of magnitude and orientation, contains most of the diagnostic electrocardiographic information. However these investigators have pointed out that comparative analysis of instantaneous vectors at fixed time intervals is not appropriate if the QRS duration differs from subject to subject. The 0.03 sec. vector of an infant with a QRS interval of 0.06 sec. will necessarily correspond to a different

Table IV. Quantitative analysis of eight instantaneous QRS vectors

Normalized QRS	Scalar amplitude (mv.) X	Scalar amplitude (mv.) Y	Scalar amplitude (mv.) Z	Spatial magnitude (mv.)	Spatial orientation (degrees) Azimuth	Spatial orientation (degrees) Elevation	Spatial velocity (mv./msec.)
1/8							
Mean ± S.D.	−0.07 ± 0.22	−0.05 ± 0.15	−0.51 ± 0.25	0.58 ± 0.26	96 ± 31	+7 ± 20	0.05 ± 0.03
Range†	−0.51 → 0.63	−0.35 → 0.27	0.00 → 1.27	0.19 → 1.50	17 → 159	−51 → +58	0.03 → 0.20
2/8							
Mean ± S.D.	0.53 ± 0.34	0.37 ± 0.40	−0.81 ± 0.80	1.22 ± 0.46	53 ± 35	+25 ± 17	0.14 ± 0.06
Range†	−0.09 → 1.33	−0.20 → 1.36	−1.80 → 1.20	0.47 → 2.44	87 → 190	−36 → +25	0.01 → 0.35
3/8							
Mean ± S.D.	1.40 ± 0.57	1.20 ± 0.46	0.18 ± 0.71	2.05 ± 0.83	354 ± 25	+45 ± 18	0.21 ± 0.10
Range†	0.18 → 2.62	0.10 → 2.40	−0.90 → 1.81	1.11 → 3.02	300 → 40	10 → 40	0.05 → 0.43
4/8							
Mean ± S.D.	0.89 ± 0.81	0.70 ± 0.73	1.10 ± 0.66	1.85 ± 0.61	299 ± 33	+25 ± 23	0.18 ± 0.06
Range†	−0.81 → 2.09	−0.90 → 2.20	0.00 → 2.04	0.75 → 2.95	270 → 1	+31 → −14	0.05 → 0.39
5/8							
Mean ± S.D.	−0.23 ± 0.32	−0.06 ± 0.38	0.91 ± 0.39	1.04 ± 0.44	250 ± 18	+7 ± 18	0.13 ± 0.07
Range†	−1.25 → 0.50	−0.15 → 1.10	0.12 → 1.75	0.22 → 2.06	240 → 330	−40 → +36	0.03 → 0.34
6/8							
Mean ± S.D.	−0.09 ± 0.20	−0.08 ± 0.16	0.31 ± 0.26	0.38 ± 0.31	200 ± 30	0 ± 24	0.06 ± 0.03
Range†	−1.16 → 0.18	−0.63 → 0.10	0.00 → 1.40	0.00 → 1.50	210 → 314	+40 → −30	0.03 → 0.13
7/8							
Mean ± S.D.	−0.09 ± 0.06	−0.04 ± 0.09	0.05 ± 0.10	0.05 ± 0.14	230 ± 36	−10 ± 21	0.04 ± 0.03
Range†	−0.41 → 0.09	−0.50 → 0.10	0.00 → 0.50	0.00 → 0.67	190 → 300	−30 → +30	0.02 → 0.13
8/8							
Mean ± S.D.	0.01 ± 0.03	−0.02 ± 0.02	0.02 ± 0.06	0.03 ± 0.06	227 ± 80	−18 ± 10	0.01 ± 0.01
Range†	−0.05 → 0.04	−0.09 → 0.00	0.00 → 0.10	0.00 → 0.34	215 → 270	0 → −30	— → 0.02
Maximum QRS vector							
Mean ± S.D.				2.45 ± 0.41	330 ± 32	+40 ± 15	
Range†				1.43 → 3.25	280 → 37	0 → 70	

*Measurements obtained each eighth of the total QRS duration.
†Limits of 96-percentile range.

state of the ventricular depolarization than the 0.03 sec. vector of a child with a QRS interval of 0.08 sec. A better approach consists of obtaining time measurements from both ends of the QRS; however, this technique might produce either an overlap or a gap in the middle of the QRS. These shortcomings are avoided by normalization of the QRS into time intervals which permit inter-individual comparisons, disregarding differences in QRS durations. The qualitative and quantitative analyses of the curves of spatial magnitude and orientation have demonstrated value in recognizing electrocardiographic abnormalities in adults.[13] The usefulness of this type of spatial data display remains to be tested in children.

The spatial velocity of the QRS. The interruption of vectorcardiographic loops at a given unit of time is considered of value for the diagnosis of intraventricular conduction defects. However, descriptions such as "terminal delay" or "slowing of the QRS" are only subjective evaluations. The introduction of curves of spatial velocity[17] permits an accurate quantitation of the directional changes of the electrocardiogram. The present study demonstrates that higher velocities are reached at the time the curve of spatial magnitude reaches its higher values. This finding calls our attention to the dependence of the calculated spatial velocity on the magnitude of the vectors.[17] For this reason, values obtained from normal hearts with normal QRS amplitudes are not comparable to those obtained from hypertrophied heart with increased QRS magnitudes. It must

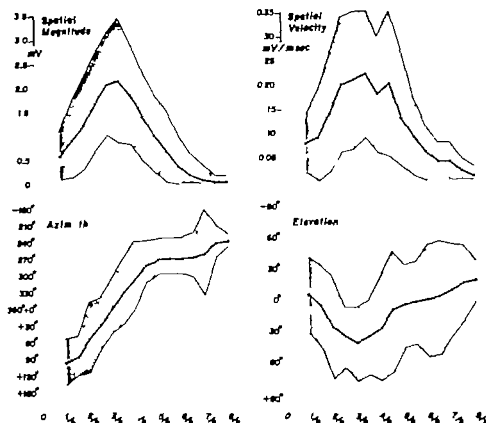


Fig. 5. Mean curves of spatial magnitude, spatial velocity, azimuth, and elevation. The shaded area indicates the 96-percentile limits.

Table V. Maximum spatial magnitude (MSM) and age, body weight, body surface, and chest circumference

Groups	No. of cases	MSM Mean	± S.D.	
Age (yrs.)				
1–4	34	2.50	0.10	
5–10	38	2.45	0.09	p < 0.90*
11–15	28	2.41	0.10	
Body weight (lbs.)				
30–75	74	2.42	0.06	
75–120	4	2.56	0.12	p < 0.75
120–150	2	2.43	0.41	
Body surf. (sq. M.)				
0.40–0.70	38	2.51	0.09	
0.80–1.10	50	2.40	0.08	p < 0.70*
1.12–1.16	12	2.50	0.17	
Chest circumf. (inches)				
18–23	40	2.51	0.09	
23–28	32	2.46	0.10	p < 0.85
28–32	28	2.57	0.11	

*Analysis of variance for complete randomized design model.

be kept in mind that the spatial velocity is not a measure of the speed of ventricular activation. Instead it reflects the rate of change in the location of the *dominant* sinks and sources of the heart currents as studied from the body surface. It has been demonstrated that the curves of spatial velocity are sensitive indicators of the presence of ventricular conduction defects and also allow an accurate quantitation of progressive degrees of right bundle branch block.

The maximum spatial magnitude and the dipole moment of the heart. The influence of age, body weight, body surface area, and chest circumference upon the MSM of the QRS in infants and children seems to have escaped general attention. Our findings demonstrate (Table V) that in normal children the MSM is not significantly affected by these variables. This is not in conflict with the results obtained in torso models, where an inverse relationship between torso size and body surface potentials was found[7] in concurrence with Hecht and Van Milaan's studies demonstrating that *the magnitude of the lead vector* is inversely *proportional* to the dimensions of the body. What the present study tends to show, rather, is that in the living subject the effective electric moment of the heart increases with body growth, thus compensating for the increments in body size. On the other hand, in the torso model studies a fixed-current dipole was used; thus, the magnitude of the potentials at the body surface was affected by the volume of the model. Recent considerations have emphasized *that the absolute magnitude of the body surface potentials can be affected by many factors acting upon the heart's dipole moment and upon the lead fields.*

Among the factors that will enhance the dipole moment of the heart during body growth, those producing an increased amount of longitudinal current generated in each heart muscle fiber and a decreased amount of internal cancellation must be taken into account. There is no evidence that the number of fibers *increases during physiologic growth*; however, it is known that the cross-sectional area of the *muscle fiber* does increase. This would probably decrease the intracellular resistance and increase the rate of polarization reversal with consequent increased amount of longitudinal current generated in each fiber. A decreased amount of internal cancellation between the ventricles probably plays a role during early infancy when the physiologic right ventricular hypertrophy disappears. This might explain in part the steady increase in MSM reported by Liebman and co-workers *in infants from birth to six months of age.*

Besides the factors directly *influencing the current dipole moment,* those which affect the heart lead relationship—such as the finite boundary effect, torso resistivity, and end-diastolic volume—must be taken into consideration in order to explain the absolute magnitude of body surface potentials. It has been demonstrated by Canfield[33] and Wilson and colleagues that the boundary between the body tissues and the surrounding air augments the magnitude of body surface potentials. The influence of the finite boundary in comparisons of surface potentials between children and adults remains to be tested. *Certain differences might be expected because of the changes in angle of curvature of the* thoracic walls during body growth. It might be anticipated that the augmentative effect of the boundary would bear an inverse relationship with torso volume. Bayley and Berry[36] demonstrated that increasing the specific resistivity of body tissue exterior to the heart produces an increase in the absolute magnitude of the body surface potentials. The demonstrated differences in torso resistivity between children and adults *and the positive linear relationship of this resistivity* with body size[illegible] *suggest that it must play a part in increasing the body surface potentials.* The effect of the intracavitary blood volume upon body surface potentials has been theoretically analyzed by Brody.[illegible] This investigator stated that the presence of the intracavitary blood mass augments the effective strength of normal components of myocardial doublets, and reduces the effective strength of tangential components. *Since under normal circumstances most of the ventricular depolarization expands in a radial direction,* Brody's observations are of the utmost importance. In previous studies done in this laboratory regarding

the effect of ventricular and end-diastolic volume upon the MSM in dogs, it was found that increasing the end-diastolic volume by one third of the original control value increased the MSM an average of 18 per cent. It is conceivable that the significant differences in end-diastolic volumes between infants and adults (13 c.c. for a child of 0.40 sq. M. body surface area, and 125 c.c. for an adult of 1.80 sq. M. body surface area[23,24]—about a 10-fold increase above the child's end-diastolic volume) must contribute significantly to the augmentation of the electric output of the myocardial fibers.

Because of the number of variables that might affect the absolute magnitude of the potentials on the body surface it seems impossible to calculate the "true electric moment" of the heart from body surface potentials only. Knowledge of the dimensions of the thorax and integration of potentials over the body surface,[25] *as well as over every interface* within the nonhomogeneous human torso must be required in order to approach the actual dipole moment of the heart.[25,26] Since this tremendous task is certainly too complicated to be accomplished by routine clinical procedures, the cardiologist, at least for the present, must rely on a practical electrocardiographic lead system that will permit accurate quantitation of the absolute magnitude of body surface potentials. Theoretical and clinical studies[3-11] have demonstrated that the lead system proposed by McFee and Parungao[8] meets the requirements of accuracy and simplicity which are desired for routine clinical use.

Summary

Corrected orthogonal electrocardiograms, obtained by means of McFee and Parungao's lead system, were recorded from 100 normal children, ranging in age from 1 to 15 years. Data from the QRS complex were analyzed by means of a digital computer.

The amplitudes and duration of the QRS deflections, as well as the curves of spatial magnitude, orientation, and velocity are presented. Correlations of the QRS amplitudes and MSM against age, weight, body surface area, and chest circumference demonstrate, in general, no significant relationship. A low but statistically significant correlation was found between both the Q wave and the Q/R ratio in the Z lead and body surface area, body weight, and age.

The authors express their gratitude to Mrs. Elizabeth Carey for her assistance in the preparation of the manuscript.

REFERENCES

1. Schmitt, O. H., and Simonson, E.: The present status of vectorcardiography, Arch. Int. Med. 96:574, 1955.
2. Burger, H. C., and Van Milaan, J. B.: Heart vector and leads. I, II, and III, Brit. Heart J. 8:157, 1946; 9:154, 1947; 10:229, 1948.
3. McFee, R., and Johnston, F. D.: Electrocardiographic leads. I. Introduction. II. Analysis. III. Synthesis, Circulation 8:554, 1953; 9:225, 1954; 9:868, 1954.
4. Abildskov, J. A., Street, W. W., Solomon, N., and Toomajian, A. H.: Clinical observation with the Frank precordial lead system, Circulation 17:1069, 1958.
5. Pipberger, H. V., Bialek, S. M., Perloff, J. K., and Schnaper, H. W.: Correlation of clinical information in the standard 12-lead ECG and a corrected orthogonal 3-lead ECG, Am. Heart J. 61:34, 1961.
6. Abildskov, J. A., and Wilkinson, R. S.: The relation of precordial and orthogonal leads, Circulation 27:58, 1963.
7. Brody, D. A.: A method for applying approximately ideal lead connections to homogeneous volume conductors of irregular shape, Am. Heart J. 53:174, 1957.
8. McFee, R., and Parungao, A.: An orthogonal lead system for clinical electrocardiography, Am. Heart J. 62:93, 1961.
9. Brody, D. A., and Arzbaecher, R. C.: A comparative analysis of several corrected vector cardiographic leads, Circulation 29:533, 1964.
10. Frank, E.: An accurate clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.
11. Duchosal, P. W., and Pasche, R.: Practical remarks on the McFee and Parungao VCG lead system, Am. Heart J. 72:287, 1966.
12. Yano, K., and Pipberger, H. V.: Spatial magnitude, orientation, and velocity of the normal and abnormal QRS complex, Circulation 29:107, 1964.
13. Ostle, B.: Statistics in research, Des Moines, 1963, The Iowa State University Press, p. 278.
14. Draper, H. W., Peffer, C. J., Stallmann, F. W., Littman, D., and Pipberger, H. V.: The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system), Circulation 30:853, 1964.
15. Linzbach, A. J.: Heart failure from the point of view of quantitative anatomy, Am. J. Cardiol. 5:370, 1960.
16. Altman, P. L., and Dittmer, D. S.: Growth, Washington, D. C., 1962, Federation of American Societies for Experimental Biology, p. 347.
17. Lepeschkin, E.: Modern electrocardiography

Baltimore 1931 The William & Wilkins Company p. 337

18. Hecht H H Some observations and theories concerning the electrical behavior of heart muscle Am J Med 30 720, 1961

19. Frimenko m, O Vevell H and Schack, J A. Comparison of good orthogonal lead system and one additional best lead with the conventional 12 lead electrocardiogram Circulation 35 146 1967

20. Rec arren S and Anas-Stella, J Growth and development of the ventricular myocardium from birth adult life Brit Heart J 26 187 1964

21. H ik tein H h and Hamlin, R QRS component of the spatial vectorcardiogram and the spatial magnitude and velocity electrocardiograms of the normal dog Am. J Card 6 1049 1960

Gamb R Gupta, D and White N Right bundle branch block and the velocity of the electrocardiogram Arch I t Med 120:286, 1967

23. Bi ne J P Spach M S and Ayers, C. R Time-normalized correlation of ventricular ... and the vectorcardiogram, Am H J 73:64 1967

24. Gamboa, R Applicability of the axial lead ... children, Am J Cardiol 18:698 1966

B k R H nd Berry P M Body surface ... duced by the eccentric dipole the ... of the nonhomogeneous volume ... Am H ART J 65:200 1963

B d I V A theoretical analysis of intra ... blood mass fluence on the heart lead relation hip Circulation Res 4 731 1956

27. Liebman, J Romberg H C. Downs, T and Agusti, R. The Frank QRS vectorcardiogram the premature infant, Proc. Long Island Jewish Hospital Symposium Vectorcardiography Amsterdam 1966, North Holland Publishing Company p. 256.

28. Canfield, R On the electrical field surrounding doublets and it significance from the standpoint of Einthoven equations, Heart 14 102, 1927

29. Wilson, F N Macleod A G and Barker P S The distribution of currents of action and injury displayed by heart muscle and other excitable tissue, Ann Arbor 1933, University of Michigan Science Series, 10.

30. Wilson, F N Johnston, F D Rosenbaum F F and Barker P S On Einthoven triangle the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram Am. HEART J 32:277 1946.

31. Gamboa, R., nd Adair B Thorax resistivity i children and adults, J Appl. Physiol. 23 107 1967

32. Gamboa, R., and Gupta, D Influence of end-diastolic volume on the magnitude of the QRS complex in dogs. In preparation.

33. Miller G. A. H and Swan, H. C. J Effect of chronic pressure and volume overload on left heart volumes in subjects with congenital heart disease, Circulation 30:205 1964

34. Kennedy J W Baxley W A Figley M M Dodge H T and Blackmon, J R Quantitative angiocardiography I The normal left ventricle in man, Circulation 34:272, 1966.

35. Nelson, C V Design of accurate vector lead systems, J Maine M A 58:5 1967

The Macruz index in the healthy newborn and infant

S. Zoe Walsh, M.D.
Stockholm, Sweden

In 1958 Macruz and associates[1] described a formula for electrocardiographic diagnosis of left, right, and combined atrial enlargement based on the ratio between P wave duration and the P-R segment. According to these authors this ratio, which is commonly referred to as the Macruz index, normally ranges from 1 to 1.6 and values above or below this indicate left atrial or right atrial enlargement, respectively. However, in patients with combined atrial enlargement, P duration and the P-R segment are prolonged and the ratio may then be normal. The ratio was calculated in children from Ziegler's[2] data and a mean of 1.2 from birth to 16 years of age was found. The conclusion was, therefore, that no significant change occurs with age.

The purpose of the present study is to determine normal values in healthy infants of normal and low birth weight.

Material and method

A total of 592 electrocardiograms (ECG's) of 68 healthy full-term and 82 healthy premature infants were studied. Tracings in full-term infants were recorded with a 4 channel jet writer at a paper speed of 100 mm. per second, while those in premature infants were recorded with a 2 channel photographic writer at a paper speed of 75 mm. per second. Readings were made with a lens of 3.5 X. Measurements of maximum P wave duration (onset of P wave to onset of P-R segment), P-R segment (onset of P-R segment to onset of QRS complex), and P-R interval were made in simultaneously recorded standard bipolar leads. In this study, P-R segment was taken as the difference between P-R interval and P wave duration. The error of measurement was 1.8 msec. for P wave duration and 3.4 msec. for P-R interval using $\sqrt{\frac{\Sigma d^2}{2(n-1)}}$

Results

In *premature* infants, differences are not significant during the first week and all values are grouped together for analysis. At this age, more than half of the infants have an index smaller than 1, while two subjects have a value greater than 1.6. The mean remains smaller than 1 until the infants are almost 3 months old, presumably because of the relatively short P wave duration and long P-R segment (Table I). There is a significant increase in index from 5 weeks to 16 months of age (regression line $y = 1.02.82 + 0.01705 \times$; $t = 2.372$; $P < 0.05$) (Fig. 1). No infant had a value above 2.5 at any time.

From the Department of Pediatrics, Karolinska Hospital, and Wenner-Gren Research Laboratory, Norrtulls Hospital, Norrtullsgatan 14, Stockholm, Sweden.
Supported by grants from the American Heart Association, National Institutes of Health (1 T01 HD 144-01) and the Association for Aid to Crippled Children.
Received for publication May 13, 1967.

*Complete data on these infants have been published elsewhere.

Table I. Findings in healthy full term and premature infants

Age	Macruz index				P duration (msec.)			
	N	M ± SD	SE	Range	N	M ± SD	SE	Range
Full-term								
1 d	68	1.45 ± 0.64	0.077	0.24 – 4.50	68	65 ± 13	2	25 – 105
2 d	68	1.23 ± 0.39	0.046	0.69 – 2.60	68	56 ± 9	1	40 – 80
3 d	68	1.13 ± 0.36	0.043	0.60 – 2.33	68	53 ± 8	1	35 – 70
5-6 d	68	1.08 ± 0.34	0.041	0.50 – 2.60	68	51 ± 7	1	30 – 65
Premature								
≤ 6 d	71	0.94 ± 0.31	0.037	0.38 – 2.50	71	45 ± 6	1	25 – 65
7-20 d	50	0.87 ± 0.25	0.036	0.50 – 1.66	50	46 ± 6	1	35 – 60
21-31 d	42	0.90 ± 0.22	0.034	0.50 – 1.42	42	46 ± 4	1	35 – 55
1-3 m	44	0.95 ± 0.27	0.041	0.61 – 2.00	44	48 ± 5	1	35 – 60
3-6 m	40	1.12 ± 0.37	0.059	0.64 – 2.16	40	53 ± 7	1	40 – 65
6-12 m	51	1.21 ± 0.45	0.063	0.72 – 2.28	51	56 ± 9	1	40 – 80
12-18 m	22	1.18 ± 0.28	0.060	0.71 – 1.85	23	59 ± 6	1	50 – 70

MACRUZ INDEX

Regression lin y 1.345987 .002274

2.6, 2.4, 2.2, 2.0, 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, 0.6, 0.4, 0.2

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170

AGE (HRS)

Fig. 1. Relation in premature infants between age and the Macruz index.

P R segment (msec.)				P R interval (msec.)			
No.	M ± SD	SE	Range	N	M ± SD	SE	Range
68	49 ± 15	2	20–105	68	114 ± 17	2	80–160
68	47 ± 10	1	25–70	68	103 ± 13	2	80–135
68	49 ± 11	1	30–80	68	10 ± 13	2	80–140
68	49 ± 11	1	25–80	68	100 ± 13	2	70–140
71	51 ± 11	1	20–75	72	96 ± 12	1	70–130
50	55 ± 12		30–80	50	100 ± 1	2	80–125
42	54 ± 11	2	30–80	4	100 ± 11	2	80–125
44	52 ± 10	2	30– 0	44	100 ± 9	1	85–120
40	47 ± 11	2	25–70	41	100 ± 11	2	5–130
51	50 ± 12	2	30–75	51	107 ± 13	2	85–145
22	52 ± 10	2	35–70	22	111 ± 12	3	90–130

Fig. 2. Relation in full-term infants between age and the Macruz index.

Mean indivi lu 1 lifferences in index were evaluated in 26 of these pr mature infants each of wh m w s examined at 1 week to 3 month 3 t 6 month and 6 month to 1 year 21 howed in inc se from the first to tl e sec nd and r tl ird of these exami nati m

The index on s lerabl larg r in *full term* than in premature infants of compara bl age whi h i prob bly due to a longer I wa e duration In these infant sig nifi ant in lex differences ccur on the fir t l s nd during the week (regressi n l ne 1 31586 ~ 0 00 214 X t = 21 092 p < 0 001 Thu an index of 1 55 or gr ater i foun l in 8 of 17 infants examined w thin the first half hour but in only 3 of 17 nfant examined after 4¼ hours of l fe (p < 0 05) Decreases in index fr m the first t the second day (r = 0 480 p < 0 001 n l f om the first to the fifth or sixth l y of l fe are als ignificant (p < 0 001 A t tal of 19 infants have a ratio of 1 6 r g e ter nitially (maximum 4 5) n l ed t 3 at the end of the week (6 p < 0 001) while 16 have 1 1 r less a compared to 37 at the l of the week (p < 0 001) (Fig 2)

M an ndi idual changes during the week were also determined From the first to tl second day of life tl e greatest de crease occurred in infants examined within the f rst half hour (mean decrease = 0 27) whil the only infants to show a mean in crease (= 0 10) were more than 4¼ hours of age initially However 55 of tl e 68 infants showed a decrease at the end of the week.

Analysis of cases with highest and lowest values on the first day of life shows that high values are associated with long I wave duration and low values with long I R segment and interval (Table II)

Moreover in these infant mean values for heart volume and systolic blood pres sure† are higher in those with a greater and lower in those with a smaller index (p < 0 05) but when all 68 infants are in cluded no d rect correlation i present

The relation hip between tl e Macruz index and variou electrocardiographic mea urements was also studied In all in tances the correlation coefficient was calculated and the t test used to evaluate the significance of the findings A positive correlation between the index and increas ing amplitude and R S ratio of the follow ing deflections was found

On the fir t d I Q₃ R T (p < 0 05)
At the end of the week I n T R₁ S₁ S₁ (p < 0 05) R/S₁ R₁ S₁ (p t short d ...ent nt)

In other words, the index appears to vary directly with voltage—in left precordial lead when mean Macruz values are high est in right precordial lead when mean values are lowest i.e at the end of the week Although tl ere i only weak sig nificance the data all point in the same direction

Discussion

Microelectrode techniques and histo logical studies suggest that normally the electrical impulse arises in the sinoatrial node and spreads along the anterior middle and posterior internodal tracts to the atrioventricular node Conduction from the sinus node to tl e left atrium i believed to occur preferentially through Bachman s bundle[4,5] Depolarization ter minates in the right atrium and then in the left atrium Although future studies of

*Using the method described by Lind
†Determined with the sphygmomanometer developed by ... worth and ...

Table II Full term infants on the fi st day of life with a Macru index either smaller than 1 or greater than 1.6 showing mean values for I wave duration P R segment P R interval and Macruz index

	No.	P duration	P R segment	P R interval	Macruz index
<1 0	10	53	72	125	0 76
>1 6	19	73	36	109	2 16

. activity of the specialized con system of the heart may modify ation of the ECG according to and associates right atrial en it prolongs the transit time from atrial node to the atrioventricular d consequently prolongs the P R and interval alters P wave con- t does not increase P wave dura cause this involves the terminal he P wave. On the other hand left nlargement primarily causes an in P wave duration which shortens segment, but as right atrial transit not affected the P R interval re normal. However combined atrial nent results in prolongation of wave duration and the P R interval index may therefore stay within limits.

es in dogs on the relationship be- normal atrial activation and the in Lead II provide some confirma- this concept The end of right atrial on never went beyond the apex of wave left atrial activation encom- most of the ascending segment and irds of the descending segment of ave but the final one third could correlated with activity of any epi- atrial point.[4]

nformation is available on the re hip between the Macruz ndex and physiologic and or autopsy meas- its in infants. In one of the few correlating hemodynamic and elec liographic observations taller P negative T waves over the left, ative T waves over the right chest commoner in newborns with higher pulmonary artery pressures. Sig t correlations between the R/S ver both sides of the chest and left it shunt and pulmonary to-system c re ratio were also noted. Although l studies relating the P wave (voltage on, Macruz index) to findings on c catheterization, angiocardiog and autopsy (atrial weight[12] and ie[13]) have been done in adults with enlargement the results are not able to nfants because changes in iction undoubtedly result from ag

) simple method permitting recog nition of atrial enlargement in early in fancy has much to recommend it. This study indicates that the range of normal variation is greater than that reported by Macruz and associates,[1] but considerably less than that noted by Pipberger and Tanenbaum[3] in healthy adults. Contrary to the estimate made by Macruz and associates,[1] from Ziegler's[2] values, changes in index occur with age in infants of both low and normal birth weight and had the series been larger the differences would probably have been greater The disparity in the number of subjects in these two groups makes it difficult to draw any con- clusion regarding differences in index dur ing the first week. A greater ratio on the first day of life was expected as P wave duration had previously been shown to be relatively prolonged at this age [5] It seems unlikely that prolongation of the P wave solely reflects the increased load on the left atrium resulting from left-to-right shunting through the ductus arteriosus because it is longest during the first hour of life and continues to decrease during the week. The gradual increase in index during the first year of life appears to parallel the increasing preponderance of the left side of the heart. Work is now in progress to evaluate this ratio in infants with congenital heart disease.

Summary

Measurements of Macruz index, P wave duration, P R segment, and P R interval were made on 597 ECG from 68 healthy full term and 82 healthy premature in fants. In full-term infants serially examined during the first week of life the Macruz index is greatest immediately after birth and then decreases significantly In pre mature infants, the index increases from 5 weeks to 16 months of age. Possible causes of these findings are discussed

Professor John Lind kindly read the manuscript and gave valuable advice The technical assistance of Mrs. Siv Lundqvist is gratefully acknowledged.

REFERENCES

1. Macruz, R., Perloff J K., and Case R. B A method for the electrocardiographic recog- nition of atrial enlargement, Circulation 17:882, 1958.
2. Ziegler R F Electrocardiographic studies in normal infants and children, Springfield, Ill 1951 Charles C Thomas, Publisher

3. Walsh S Z I olut on of the elect oc rdiogram of be lthy premature nf t during the fir t ar f lif Act paediat Suppl 145 1963
4 I nd, J H art lume in normal inf t Act hol Suppl 8 1950
5 Ashw rth, A M N lig n, C A nd R ger J L Sph gm oma ome er f the newb n, Lanc t 1:801 1959
6 J mes T N The onnecting p th y be t ee the node nd AV node nd be t een the ght nd left t m the h ma heart Am H rt J 66 498 1963
7 A salle M nd H ffm B F The pread f si act t on d m pot ssium admin tion Circul t on Res 1 u85 1963
8 Sod P II res D New b ses f lectrocardi g ph St L u 1956 The C V M by Com pany p 370
9 I mamoulakes C C M s, A J and Adams, F H The lectr ard g m in normal new I f t rrel t n w th hem dynamic bserva ons, J Ped t 6 1578 1965
10. Herm n, C I nd Snyman, H W : The value f the Macru Index in the d gnos of atrial enlargement Circulation 26:935 1962
11 Arvid son, H Zaro, S nd Grewin, K E : C rrelation between m tr l P w ve nd left trial v lume determined by angiocardiog phy Card Acta 27:255 1960
12. M dend, A W lff R., W lff L., nd Reiner L C rrelat on bet een component card ac weight nd lect c rd gr phic pattern in 185 ases, Circ l t n 30 918 1964
13 I ssalo, A Teahunen A Sa f L nd Heni aa O Ev lu tion f Macru Index b sed n p tmortal atrial me urements, Act p th & micr biol. scandin v 54 301 1962
14 Lepeschkin? Hegeberger H A nd Tane baum, H L The I w v I R interv l, and Q-T r tio of the normal orthogon l lectrocardiogr m, Circul tion 10 1173 1955
15 W l h, S. Z The I w ve dur tion nd the I R interval during the first week f lif B t H art J 25 12, 1963

Beat to beat and observer variation of the electrocardiogram

Eugene Fischmann, M.D.
John Cosma, M.D.
Hubert V. Pipberger, M.D.
Washington, D. C.

Electrocardiographic measurements vary from observer to observer, from reading to reading, from one recording to another, from beat to beat, and from one patient to another. Although discussed by Kossmann in 1938, inter- and intraobserver variations have only recently received adequate attention.[2-4] Attempts at their reduction by the use of codes, careful definition of ECG signs, technician training, averaging of several readings, preferably by several readers, test records, frequently repeated variation checks, distribution of records from several sources to all readers, and computer methods are still more recent.[5-9] Some information concerning ECG variation in records repeated in the same patient at intervals of one week to a year[5] and within half an hour[3] is also available. Beat-to-beat variation (BBV) in the same record has so far not been systematically explored.

The aim of the present study is to determine the observer and BBV of selected scalar and spatial ECG measurements. This should assist in estimating desirable and attainable ECG measurement accuracy for studies of induced ECG changes and help to assess the significance of normal-abnormal differences. The BBV of wave end points should in part determine the acceptable error in the automatic recognition of the points of onset and ending of electrical activity. It is customary in current practice to use a single number to indicate a measurement in a given record, when a range including the various categories of variation would be more appropriate.

Materials and methods

A total of 58 orthogonal (Frank system) ECG's were selected at random from our magnetic tape library (Table I). In each patient a 5 in. 1 mv. digital computer plot of nine consecutive beats was obtained on 15 in. wide paper, where time and X, Y, and Z voltage were indicated at 4 msec. intervals. P onset and end, QRS onset and end, and T end were identified by hand in the digital plot and punched on IBM cards. Using these points and the taped digital ECG record, a computer print-out of the following was obtained: (1) P and QRS duration and P-R and Q-T intervals, (2) amplitude and duration of individual deflections in each of the three orthogonal

From the Veterans Administration Research Center for Cardiovascular Data Processing and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.
Supported in part by United States Public Health Service Research Grant from the National Heart Institute (HE [illegible]).
Received for publication May 18, 1967.
Present address: Cardiology Department, The Hospital for Sick Children, 555 University Avenue, Toronto 2, Ont., Canada.

Table I. Elect oc1 diogr1phic diagnosis in 58 patient

ECG diag m	N f patient
Norm l ECG	29
R gh rn lar hypert ph	3
Lef en lar h pertroph	5
B en l h pertrop h	3
R ght tric lar cond on defect	2
L ft tric l ndu on defect	1
A t sept l MI	5
P eroduphragmat MI	1
S tach rd	2
Wolff P kinson Wh ndrome	1
T l	58

lead (3) magn tude and lirection of five set of inst nt neou QRS vectors 0 01 0 0 0 03 0 04 nd 0 05 sec after the onset and bef re th end ng of QRS and before a d fter th peak of R n Lead X re pecti l (4) magnitude and direction of th m x al patial QRS vectors.

A t t l of 522 values w re availal le for ach it m for the ev luation of BBV. M x n l be t to-beat variation (BBVm) w s ol tained as follows Since we had 9 be t n each of 58 patient the mean of the 9 values and the d viation fro the mean wa calculated for ea h c se. The deviations were then pooled for all cases and the 96 percentiles and mean of the pooled values were tabulated

In order to study observer variation four observers received the computer plots of the 58 pati nts. Two of the observers were physicians and two were technicians. All four readers were experienced in vi ual wave recognition. Each observer marked the onsets of P and QRS and the end points of P QRS and T in 2 beats in each of the 58 records. Each ECG was read twice by each observer. The times of wave onsets and endings indicated by the four observers were punched on IBM cards. The durations of P P R QRS and Q-T in tervals were calculated by a computer and the variation in these time measurements was used as an indicator of f rst to-second beat observer variation and of repeat varia tion on re-reading the same beats. The

Table II. M ximal beat to-beat v r iation of spatial QRS vectors and scal r d flection amplitudes (9 beats)

Mea ement	BBVm (mv)†
M gnitudes f patial ec to rs QRS ectors	
0 01 sec after onset of QRS	0 10
0 02 sec af nset of QRS	0 18
0 03 sec after onset of QRS	0 31
0 04 sec after onset of QRS	0 41
0 05 sec fter onset of QRS	0 28
0 05 sec bef re end of QRS	0 42
0 04 sec bef end of QRS	0 43
0 03 sec b f re end of QRS	0 28
0 0 sec before end of QRS	0 11
0 01 sec bef re end of QRS	0 07
0 04 sec b f re pe k of Rx	0 05
0 03 sec b f re pe k of Rx	0 05
0 0 sec bef re pe k of Rx	0 10
0 01 sec bef re pe k of Rx	0 20
0 01 sec fter pe k of Rx	0 19
0 02 sec ft pe k of Rx	0 16
0 03 sec fter p k of Rx	0 10
0 04 sec fter pe k of Rx	0 08
Scal lead amplitud	
Q mpl tude	0 03
Q amplitude	0 05
Q amplitude	0 03
R mpl tude	0 05
R amplitude	0 06
R mpl tude	0 05
S amplitude	0 04
S ampl tude	0 05
S mplitude	0 05
M g tude of ma imal patial QRS ector	0 08

For ach me surement, he mean of he available values in rec rd, and he deviations f om he mean were deter mined. All deviations f r 58 records (58 × 9 = 522) ere pooled.
†M + 2 S.D. of the p led deviations

means and 96 percentiles of the ranges of variation obtained were calculated The performance of physicians and technicians as groups was also compared

Results

Amplitude BBV of scalar lead deflections The Q R and S peak amplitude BBVm of Leads X Y and Z ranges from 0 03 to 0 08 mv giving a mean of 0 05 mv for th group (Table II Fig 1) Its absolute

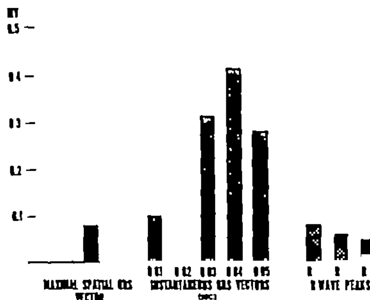


Fig. 1. Maximal BBV of three groups of ECG measurements. In each patient 9 measurements from 9 consecutive beats were available. The mean of each set of 9 values and the 9 deviations from the mean were computed. The deviations (58 x 9 = 522) were pooled for each measurement and BBVm in millivolts expressed as the mean + 2 standard deviations of the pooled deviations. The peak values shown represent, therefore, the extremes of beat-to-beat variability.

BBVm is thus the lowest of any group of scalar measurements examined. Of the 9 BBVm measurements in this group 7 are 0.05 mv or less. Absolute S and Q variation tends to be less than that of R.

BBV of spatial vector magnitudes. BBVm of the magnitudes of the P, QRS, and T maximal spatial vectors were 0.08, 0.12, 0.10 mv, respectively. The mean BBV of these vectors was 0.03, 0.03, and 0.04 mv (Table IV).

The BBVm of spatial instantaneous vectors (Table II) when QRS onset or end was the time reference, ranged from 0.07 to 0.43 mv, around a mean of 0.26 mv. Using the peak of R_x for time reference, BBVm of instantaneous vectors decreased ranging from 0.03 to 0.20 mv, around a mean of 0.10 mv, closely approaching the BBVm of maximal spatial vectors. In Table II the BBVm of 14 of the 20 instantaneous spatial vectors exceeded the largest scalar lead amplitude BBVm (0.08 mv). Using R_x as a reference only 3 of the 10 vector magnitudes obtained showed a maximal BBV greater than 0.01 mv (Table II). None of the R_x reference vector BBV magnitudes exceeded 0.02 mv. Only the 2 smallest 0.01 msec. vector magnitudes of the QRS onset QRS end set of instantaneous vectors approached the 0.08 mv BBVm of the maximal spatial QRS vector whereas 7 vectors of the R_x reference series were close to it, 3 equal it, and 2 (0.05 and 0.06 msec., respectively) were smaller. These two magnitudes, 0.05 msec. before and after the R_x peak, showed the smallest BBVm of any spatial vector magnitude recorded in the present study.

The millivolt values of BBVm were greater in the large midtemporal vectors than near the beginning and end of QRS regardless of whether the onset or end of QRS or the peak of R_x was the zero reference (see Tables III and IV).

BBVm of the direction of spatial vectors (Table V). The spatial instantaneous QRS vectors showed a wider range of directional BBVm than the maximal QRS vector and in the large midtemporal QRS vectors the R_x reference again resulted in a reduction of BBVm. In the small early and late QRS vectors directional BBVm remained large regardless of the choice of the point of reference. Unlike the BBVm of spatial vector magnitude where some of the more

Table III. Maximal beat-to-beat variation. Groups of measurement (9 beats)

Measurement	BBV m (mv)
QRS single deflection amplitude	0.05
Maximal spatial QRS vector magnitude	0.09
Instantaneous spatial QRS vector magnitudes	
0.01 to 0.05 sec. after QRS onset	0.[illegible]
0.05 to 0.01 sec. before end of QRS	0.26
0.05 to 0.01 sec. before peak of Rx	0.10
0.01 to 0.05 sec. after peak of Rx	0.11
Multitemporal instantaneous spatial QRS vectors	
0.01-0.05 sec. from QRS onset and end and 0.01-0.02 sec. before and after Rx peak	0.38
Early and late instantaneous spatial QRS vectors	
0.01-0.0 sec. from QRS onset and end, and 0.01-0.03 sec. before and after the peak of Rx	0.09
Maximal QRS spatial vector direction	7°

*For each measurement the mean of the available 9 values [illegible] and [illegible] deviations from the mean were determined. All deviations in the 38 records were pooled. †Mean + [illegible] of the pooled deviations.

Table IV. Mean and maximal beat-to-beat variation of maximal spatial vectors and time measurements

	Duration or interval (msec.)		Maximal spatial vector (mv)	
	Mean	96 per cent	Mean	96 per cent
P	19	37	0.03	0.09
P-R	8	33		—
QRS	6	19	0.01	0.12
Q-T	12	65		—
T			0.01	0.10

stable instantaneous vectors approached the standard of stability of the maximal spatial vector, the directional BBV m of instantaneous vectors did not approximate that standard.

Beat-to-beat and repeat observer variation (*Table V and Figs. 2 and 3*). QRS duration showed the least (both mean and 96 per cent) repeat and beat-to-beat variation. Q-T duration, with the single exception of the two-physician mean, showed the greatest. The technician group showed on every score less variation than physicians (Fig. 3). In the more consistent technician group, mean repeat variation was less than mean beat-to-beat variation. This applied also in all but two instances of mean data (four observer and two physician means of QRS duration) in the other group. The exceptions were the four observer and two physician means of QRS duration, where repeat and beat-to-beat variation were equal. In no instance was the mean repeat variation less than the mean beat-to-beat variation.

In the technician group the mean variation of P duration and P-R interval approximated each other closely. In three out of the four remaining instances, mean P-R interval variation was less than the mean variation of P duration.

Discussion

The reported observations on beat-to-beat and observer variation were obtained from orthogonal ECGs. Since they do not depend on any particular type of ECG lead, comparable findings may be expected from any other set of leads. The choice of large computer plots without appreciable base-line thickness tended to reduce the observed BBV. In conventional recordings the choice of upper or lower border of the baseline for amplitude measurements can affect results seriously and become an additional source of observer variability.[14]

Causes of BBV. Inferior QRS shift in inspiration and superior shift in expiration is the most common cause of BBV. A sequence of nine heartbeats was chosen for the study in order to include at least two respiratory cycles. No attempt was made to separate the respiratory changes from the BBV due to other causes. Three of the six cases with ventricular conduction defect presented BBV at the upper extreme of the observed ranges. Cardiac forces in intracardiac conduction defects seem not only abnormal in magnitude and direction but also abnormally unstable. Normal and abnormal patients did not differ with regard to BBV. Noise base-line shifts of

Table V. Mean and mean + 2 S.D. of beat-to-beat variation of the direction of instantaneous spatial QRS vectors

Instantaneous QRS vectors (sec.)	*After onset of QRS*	*Before end of QRS*	*Before peak of Rx*	*After peak of Rx*
0.01	25° 77°	28° 78°	6° 20°	6° 16°
0.02	17° 57°	25° 83°	9° 31	6 20°
0.03	16° 52°	17° 63°	15° 43°	10° 32°
0.04	11 37°	14 46°	24 70°	18° 56
0.05	9° 27°	13° 43°		

Table VI. Observer variation: two physician and two technician readers

	4 observers		2 physicians		2 technicians	
	Mean	96 per cent	Mean	96 per cent	Mean	96 per cent
Repeat reading variation						
P duration	6	40	12	46	4	24
P-R interval	7	32	10	38	5	20
QRS duration	6	26	8	32	3	16
Q-T duration	10	48	4	59	6	44
First to second beat variation						
P duration	11	32	15	26	7	18
P-R interval	9	32	11	38	7	24
QRS duration	6	24	8	22	5	18
Q-T duration	12	36	13	40	9	26

Measurements in milliseconds (msec.).
Repeat reading variation: Two beats in each of the 58 records were read and re-read by four observers, yielding 116 pairs of readings for each observer. The differences between the first and second readings were pooled for four observers, two physicians and two technicians, respectively. The means and 96 per cent maxima for each of the three groups are shown.
Beat-to-beat variation: Readings were regrouped to form 116 pairs, each pair consisting of one first beat and one second beat reading in the same record. The first to second beat differences within pairs were again pooled for four observers, two physicians and two technicians, and means and 96 per cent maxima of the ranges are shown.

brief duration or rapid transients induce BBV by changing the onset or ending or the amplitude of the ECG deflections, especially early and late in QRS.

Spurious BBV. In two cases (6 beats) small initial or terminal QRS vectors, which were almost perpendicular to the plane under study, showed planar shifts approaching 180 degrees with only a minor change in spatial direction. Some loop configurations facilitate a spurious BBV of the maximal QRS vector in projection planes. In Fig. 4,A the 80 and 160 msec. points correspond to vectors with almost identical spatial magnitudes, so that the maximal vector easily changes from one to another, resulting in the largest directional and smallest magnitude variation in the present series. In Fig. 4,B the 40 and 60 msec. vectors alternate as maximal vectors.

The three orthogonal leads further elucidate the mechanism of the spurious vector shift in these two cases. In Fig. 4,A each of the Leads X, Y, and Z show QRS peaks of approximately equal amplitudes, widely separated in time. Relatively slight BBV in the amplitudes of the peaks will therefore move the 3 lead QRS maximum from one peak to another. In Fig. 4,B the

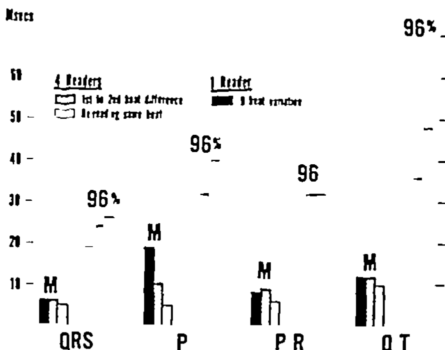


Fig. 2 Comparison of 9-beat HBV of one reader with beat-to-beat and repeat variation of four observers. Each observer marked P and QRS onset and P, QRS, and T ending on each of 58 2-beat computer plots. This was repeated independently [illegible] second identical plot yielding 116 2-beat readings for each observer. The variation [illegible] P and QRS duration and P-R and Q-T intervals determined by digital computer from the visually identified [illegible] the measure of variation. Beat-to-beat and rereading differences were pooled for the four observers and the means and 96 percentiles of the pooled values are shown. Time intervals and durations [illegible] determined in the 9-beat plots read by a single observer. The means and 96 percentiles of the [illegible] deviations for each measurement are shown.

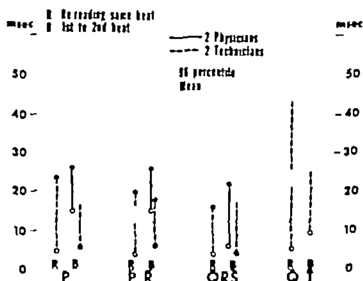


Fig. 3 Physician and technician consistency of visual ECG wave end point recognition [illegible] digital computer plots. Each of four observers marked the P and QRS onset and the P, QRS, and T ending in 2 beats [illegible] each of 58 records. This was repeated independently in a second identical plot resulting in 116 2-beat readings for each observer. Labeling was recognition based on the visually identified end points. The P and QRS duration and P-R and Q-T intervals were determined by digital computer for each beat. The variation of time intervals was used as a measure of observer consistency by pooling first to second beat and first to second reading differences for two physicians and two technicians, respectively. The mean and 96 percentiles of the pooled values are shown.

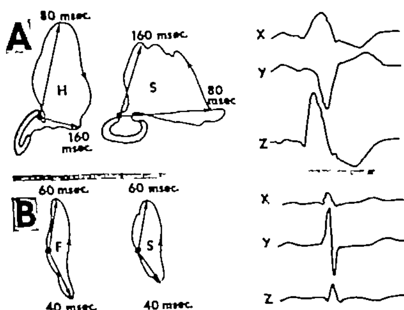


Fig. 4. Spurious large shifts of azimuth and elevation (*A*), and of elevation (*B*) of the maximal spatial QRS vector in the presence of 2 vectors of similar magnitude widely separated in time and competing for the role of maximal vector.

competing amplitude maxima are again widely separated in time, although they both appear in Lead Y. In these two cases, what seemed a change in the direction of a maximum spatial QRS vector was in fact the alternation of several large QRS spatial vectors separated in time.

BBV related to measurements. In Tables II to V it becomes obvious that BBV depends largely upon the measurements used. In parts of the QRS complex with a rapid rate of change (e.g. upstroke and downstroke of R waves) even a small change in time leads to a substantial change in amplitude. Maximal BBV parallels, therefore almost exactly spatial velocity of QRS[13] with a rapid increase toward the midportion and a subsequent decline toward the end. The spatial maximum QRS vector showed the least variation in both magnitude and direction followed by the somewhat greater BBV of scalar orthogonal lead deflection peaks and by the still greater BBV of timed instantaneous spatial vectors. This order of grouping corresponds to a grouping in ascending order of dependence on wave end point recognition. Maxima are independent of timing and thus not affected by wave end point recognition while instantaneous vectors are so affected. Maximal BBV was shown in order to emphasize the extent of BBV which may be encountered in average ECG's. The means of BBV are usually close to 30 per cent of the 96 percentile limit with a skewed distribution curve toward higher values (Tables IV-V).

Practical effect of BBV. It is usual to designate each measurement (say Q duration) by a single number. A minimum and maximum derived from several beats would be more appropriate. Also it would seem preferable to choose from measurements of related information content those with greater beat-to-beat stability. Thus Q/R ratios which exhibit great beat-to-beat stability were found markedly superior to Q wave duration measurements in the recognition of myocardial infarcts.

The R wave deflection in Lead X was tested as a point of reference for timing instantaneous vectors yielding a considerable decrease in BBV of most instantaneous vectors (Tables II, III, V). Such a reference however may lead to some new problems. The well known shift in time of the R_X peak in ventricular hypertrophies leads to a concomitant shift of the time reference which needs to be taken into consideration. The R_X peak or the maximal

spatial QRS vector may be preferable for this purpose.

Averaging measurement by computer, preferably over a complete respiratory cycle, would overcome some of the BBV. Averaging of measurement is preferable over averaging complete wave forms or complexes because the latter procedure may thus out detail.

Observer error. The use of the Minnesota Code eliminates observer variation due to clinical interpretation but not that due to inconsistency in defining an ECG wave and in applying the definition during analysis. Visual definition of a minimal base-line slope indicating deflection end point is arbitrary and variable since the observer cannot keep his standard of a criterion completely constant, unlike computer methods using fixed criteria.

In this study of observer variability of ECG measurements, even the least variable QRS duration differed by a mean of 6 msec. when read a second time by the same observer, with a 96 percentile of 26 msec. P wave onset and P and T wave endings varied considerably more due to their more gradual transition into the base-line. The consistency of technician measurement was markedly higher than that of the two cardiologists, confirming similar studies of other authors.

In longitudinal epidemiologic studies or in investigations of changes induced by pharmacologic or other agents, unless BBV is exceeded observed changes may be insignificant.

Summary

The BBV of selected ECG measurements was studied in an all male series consisting of 29 subjects with and 29 without heart disease. Nine consecutive beats of each of the 58 3-lead orthogonal records, selected to show minimal base line disturbance, were converted by computer into enlarged digital plots. A single reader manually marked P and QRS onsets and P, QRS, and T endings in the plots, and the timing of these 5 points, punched on cards, was fed to a digital computer to obtain the measurements required for the BBV comparison. Two beats in each record, independently marked on two consecutive occasions by two physician and two technician readers, were similarly processed to supply information concerning beat-to-beat and repeat observer variation.

BBV of instantaneous vectors increased with the spatial velocity of QRS and was therefore greatest in the QRS midportion. It varied also with the dependence of a measurement on QRS end point recognition, so that spatial maximum vectors showed the least, instantaneous vectors the greatest, and scalar lead amplitudes intermediate variation. Using the peak of R_X for time reference instead of the less well defined QRS end points reduced BBV. The four observer beat-to-beat variation approximates the 9 beat single observer BBV. Inconsistent wave recognition is an important cause of BBV.

Other factors causing BBV are respiration, aberrant conduction, other so far unelucidated physiologic factors, base-line shifts, and rapid transients within ECG complexes.

Occasionally, in loops with two or more widely divergent near-maximal vectors, extreme spurious BBV appears when the maximum keeps changing from one of these vectors to another. In the presence of spatial vectors, which are near perpendicular to one of the three planes, small BBV of the spatial vector may result in extreme BBV of its planar projection. Spatial vectors are, however, not affected by this type of error.

Two technicians performed wave end point timing more consistently than two physician readers.

REFERENCES

1. Kossmann, C. E.: Normal electrocardiograms, Circulation 8:920, 1953.
2. Davies, L. G.: Observer variation in reports on electrocardiograms, Brit. Heart J. 20:153, 1958.
3. Acheson, R. M.: Observer error and variation in the interpretation of electrocardiograms in an epidemiological study of coronary heart disease, Brit. J. Prev. Soc. Med. 14:99, 1960.
4. Segall, H. N.: Electrocardiogram and its interpretation: Study of reports by 20 physicians on a set of 100 electrocardiograms, Canada M. A. J. 82:2, 1960.
5. Epstein, F. H., Doyle, J. T., Pollack, A. A., Pollack, H., Robb, G. P., and Simonson, E.: Observer variation in interpretation of electrocardiograms, J.A.M.A. 175:847, 1961.
6. Gorman, P. A., Calatayud, J. B., Abraham, S., and Caceres, C. A.: Observer variation in

interpretation of the electrocardiogram, M. Ann. District of Columbia 33:97 1964.
7 Blackburn, H. The electrocardiogram in cardiovascular epidemiology Problems in standardization, Ann. New York Acad. Sc. 126:882 1965
8. Rose, G. The coding of survey electrocardiograms by technicians, Brit. Heart J 27:595 1965
9 Kagan, A. R. I terpretations of electrocardiograms, Milbank Mem Fund. Quart 43 (Part 2) 40, 1965
10 Simonson, E., Brozek, J and Keys, A. Variability of the electrocardiogram in normal young men, Am Heart J 38:407 1949
11 Fischmann, E. J Seelye, R. N and Crutcher L. R. Clinical trial of balsa-lithium electrode for conventional electrocardiography Am. J Cardiol. 10:546, 1962
12. Pipberger H. V Stallmann, F W Yano, K., and Draper H W Digital computer analysis of the normal and abnormal electrocardiogram, Progr Cardiovas. Dis. 5:378, 1963.
13. Draper H. W Peffer C. J Stallmann F W Littmann, D and Pipberger H. V The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system), Circulation 30:853 1964.
14. Cosma, J Levy B., and Pipberger H V The spatial ventricular gradient during alterations in the ventricular activation pathway Am. Heart J 71:84, 1966.
15 Yano, K., and Pipberger H V Spatial magnitude, orientation, and velocity of the normal and abnormal QRS complex, Circulation 29 107 1964.
16. V al, L A., Cosma, J and Pipberger H. V Re-evaluation of the Q-wave in the electrocardiographic diagnosis of myocardial infarction, M Ann. District of Columbia 36:349 1967
17 Blackburn, H. W Keys, A., Simonson, E., Rautaharju, P and Punsar S The electrocardiogram in population studies, Circulation 21 1160, 1960.

Different effects of increased volume and increased pressure on endocardial structure in hearts with atrial septal defect

Kyozo Okada, M.D.
Seymour Glagov, M.D.
Maurice Lev, M.D.
Chicago, Ill.

Both the absolute and relative quantities of endocardial collagen, elastin, and smooth muscle vary from site to site in the normal human heart. However, for any given site and age, the thickness, composition, and architecture of the endocardium are remarkably constant.[1] Modifications of the normal pattern of distribution of endocardial fibrous and cellular components are associated with systemic or focal disturbances of connective tissue metabolism and with congenital or acquired departures from normal cardiac blood flow and/or chamber pressure. Some of these structural changes are considered to reflect long-term responses of the endocardium to mechanical stimulation. Ridges and pockets at presumed sites of impact by blood stream or jets are composed of connective tissue with little or no vascularization.[1, 13] Zonal or diffuse endocardial fibrocellular proliferation or fibroelastosis in dilated hearts may reflect endocardial adaptation to increased mural tension.[21] The histologic features of the diffuse changes are variable. In some locations fibrous elements predominate; in others, smooth muscle hyperplasia and hypertrophy is the striking feature. Such differences in architecture and composition could be due to differences in the nature, duration, or rate of development of long-term endocardial stresses.[1]

Alterations of the endocardium are commonly noted in hearts with congenital anomalies; corresponding quantitative clinical data concerning cardiac output and chamber pressures are frequently available for such hearts at the time of autopsy. Correlation of endocardial changes with antemortem hemodynamic data could help to elucidate the mechanisms by which physical factors influence the proliferation and differentiation of endocardial tissue. To this end, we have studied and characterized endocardial changes associated with several congenital heart disease entities in the light of available catheterization

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research, and the Departments of Pathology of the University of Chicago School of Medicine, The Northwestern University Medical School, and the University of Illinois College of Medicine, Chicago, Ill.
Supported in full by Grants 4 PO1 HE 07605-[illegible] and 5 T1 HE 5339-04 from the National Heart Institute of the National Institutes of Health, Bethesda, Md.
The work of Dr. Glagov was done during the tenure of an Established Investigatorship of the American Heart Association.
Received for publication May 24, 1967.
Address: The Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

data. The findings will be reported in a series of communications.

The present report is concerned with endocardial changes in hearts with atrial septal defect of the fossa ovalis (secundum) type. Alterations associated with large shunts and normal or moderately elevated right ventricular pressures are compared with those noted in hearts with smaller shunts and high pulmonary pressures. It will be shown that there are characteristic, consistent and distinct patterns of endocardial thickening and composition associated with each of these functional states. Dilated chambers associated with large atrial shunts and normal or moderately elevated right ventricular pressure levels show increased deposition of layers of endocardial collagen and elastin, focally in the subendothelial layer and diffusely in the musculoelastic layer by contrast, enlarged chambers with smaller shunts but higher pressures show marked hypertrophy of the smooth muscle component of the musculoelastic layer

Materials and methods

Seven hearts with atrial septal defect of the fossa ovalis (secundum) type from the research specimen collection of the Congenital Heart Disease Research and Training Center form the basis of this report In six cases, cardiac catheterization had been performed one week to two months before surgical closure of the defect and two weeks to two months before death one of the individuals had no surgery and was catheterized one week before death

The cases could be separated into two groups with respect to the level of pulmonary artery or right ventricular pressure (Table I) Four patients had relatively low pressure ranging from 20 mm Hg systolic and 10 mm Hg diastolic to 45 systolic the mean systolic pressure in this group was 38 mm Hg the mean diastolic 13 mm Hg left to right shunt flow in these hearts ranged from 7 10 to 17 2 L. per minute (mean 13 7 L. per minute) The other three individuals had pressures ranging from 60 to 73 mm Hg systolic and 26 mm. Hg diastolic. Mean systolic pressure of these patients was 72 mm Hg and diastolic, 26 mm Hg left to right flow through the defect was relatively small estimated at 2 03 to 3 44 L. per minute. The group with relatively low pulmonary artery pressure but high shunt flow was called the *flow* group. The group with higher pressures but relatively small shunt flow was called the *pressure* group.

All of the heart chambers had been opened by prosectors before fixation and the valve circumferences and chamber wall thicknesses recorded After fixation in 10 per cent formalin for several days to several weeks the hearts were brought to the Congenital Heart Disease Research and Training Center and incorporated into its research specimen collection. Upon receipt, the specimens were re-examined and a series of measurements of chamber size atrial and ventricular wall thickness

Table I. Catheterization data for hearts with atrial septal defect

Group	*Age (yrs)*	*Sex*	*Pulmonary artery pressure (mm Hg)*	*Shunt flow (L/min)*	*Stroke volume left ventricle (ml)*	*Pulmonary flow (L/min)*	*Systemic flow (L/min)*
Flow	20	F	20/10	16 73	244	19 48	2 5
	38	F	37/16	17 24	269	23 0	6 46
	48	F	41/14	13 80	259	19 9	6 10
	47	M	45	7 10	147	9 8	2 70
Pressure	0 3	M	60	small	—	—	—
	38	M	71/26	3 44	81	6 63	3 19
	44	M	73/26	03	65	6 49	4 46

Right ventricular pressure

and valve dimensions were made by a member of the staff according to a standard method described in detail elsewhere.[17] In an attempt to take account of possible variation introduced by different fixation times, the measurements were repeated by one of us (R. O.) before the hearts were sampled for histologic study. No significant deviations could be detected from 3 months to 1½ years after acquisition of the hearts.

Endocardial thickening was estimated subjectively by two observers on the basis of surface opacification or "whitening" and on gross and microscopic measurements of the endocardial layer on multiple sections through the endocardium. Micrometric estimations of endocardial thickness were made on the histologic preparations of the samples taken at the standard positions listed below. These data were used to compose maps of the distribution of endocardial thickening for each of the heart chambers.

Adequate control material was available only for the adult hearts in the series. Quantitative data are therefore presented for the three adults in the *flow* group (ages 38, 47, and 48) and the two adults in the *pressure* group (ages 38 and 44). A total of 27 normal hearts from adults in the same age range served as the basis for comparison.

Alterations in the composition and architecture of the endocardium were evaluated on microscopic sections. Tissue samples were taken at the following sites: cardiac orifices of the superior and inferior venae cavae and pulmonary veins, limbus fossae ovalis, basal portions of atria and ventricles including valve leaflets and fibrous rings, interventricular septum, free walls of all chambers, papillary muscles, ventricular apices, aortic and pulmonary coni including the semilunar valves and the proximal segments of the great vessels. A total of 27 tissue blocks were sectioned for each heart. Paraffin sections 7 μ thick were stained with hematoxylin and eosin and with the Weigert–van Gieson and silver impregnation methods for connective tissue. The periodic acid–Schiff reagent and the dialyzed iron methods were used for the demonstration of acid mucopolysaccharides. Selected paraffin sections of the basal portions of the atria and ventricles, the interventricular septum, and the aortic and pulmonary coni were stained with azur A and toluidine blue to show metachromatic substances; adjacent tissue blocks were used to prepare frozen sections which were stained with Sudan IV to demonstrate fat.

Results

Qualitative and quantitative deviations from the normal pattern of adult endocardial structure were noted in all of the hearts with atrial septal defect (ASD). However, there were striking differences in both gross distribution and microscopic appearance of endocardial thickening between hearts of the *flow* group (large left to right shunts and relatively low pressures) and those in the *pressure* group (relatively small shunts and higher pressures).

Distribution of endocardial thickening. The distribution of endocardial thickenings in the normal adult hearts were the same as has been reported elsewhere.[1-4] Endocardial thickness ranged from ? to ?50 μ in normal right atria and ventricles and from 2 μ to ?.0 mm in right atria and ventricles of hearts with atrial septal defects. An endocardial width between 20 and 50 μ was termed "slight" thickening, while a width of 50 to 400 μ was called "moderate" thickening; values in excess of 400 μ were called "marked" thickening.

Departures from normal thickness and composition of the endocardium in the abnormal hearts were most marked in the right-sided chambers. Except for striking and characteristic modifications of the mitral valve and the immediately adjacent endocardium, there was little deviation from normal in the left atrium or ventricle. The valvular changes associated with atrial septal defect are treated in a succeeding report.

In Figs. 1 to 4 the gross appearance of the endocardium of the right atrium and the right ventricle is shown in photographs of typical specimens from the *flow* group (Figs. 1 and 2) and the *pressure* group (Figs. 3 and 4). Composite diagrammatic maps of endocardial thickening for normal hearts, ASD with high shunt flow (*flow* group) and ASD with high pulmonary artery pressure (*pressure* group) are shown

Figs. 1–4 Gross appearance of the endocardium in the right atria and ventricles in hearts with atrial septal defect. Arrows indicate particularly prominent zones of thickening.

Fig. 1



Fig. 2



Fig. 3.



Fig. 4



Fig. 1 Atrium and ventricular inflow tract of typical heart from the group with greatly elevated shunt flow and relatively low pulmonary artery pressure (*flow* group). The atrial endocardium is diffusely opacified; the ventricular endocardium is focally markedly thickened.

Fig. 2. The apical, lateral wall and outflow tract endocardial linings of the ventricle of the same heart shown in Fig. 1 are focally thickened.

Fig. 3 Atrium and ventricular inflow tract of typical heart from the group with relatively low shunt flow but greatly elevated pulmonary artery pressure (*pressure* group). Atrial endocardial opacifications are prominent but focal. The ventricular endocardium is also focally thickened but much less than that seen in hearts of the *flow* group.

Fig. 4 In the ventricular outflow tract of the same heart as is shown in Fig. 3 endocardial thickenings are focal and less marked than those seen in hearts of the *flow* group.

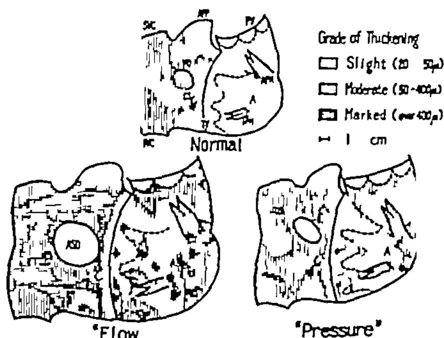


Diagram 1. Composite maps of the distribution of endocardial thickening in the right atria and ventricles of normal adult hearts and in hearts with atrial septal defect. Flow = atrial septal defect associated with increased flow and relatively low pulmonary artery pressure. Pressure = atrial septal defect associated with ... flow and markedly elevated pulmonary artery pressure. A, Apex; APM, anterior papillary muscle; APP, auricular appendage; ASD, atrial septal defect; CS, coronary sinus; FO, fossa ovalis; IPM, inferior papillary muscle; IVC, inferior vena cava; PV, pulmonic valve; SVC, superior vena cava; TV, tricuspid valve.

In Diagram 1 the relative size of the diagram reflects the relative size of the chambers.

RIGHT ATRIUM. The normal right atrial endocardium was moderately thickened about the caval orifices, along the septum over the limbus of the fossa ovalis, and at the superior edge of the crista terminalis. It was slightly thickened in the zone between the caval orifices and over the remainder of the crista terminalis. The endocardium lining the auricular appendage was extremely thin. One half to two thirds of the normal right atrial endocardium was grossly transparent.

In hearts with ASD in the *flow* group the right atrial endocardium was diffusely and markedly thickened so that at least three fourths of the total endocardial surface had become opacified. The changes included both an accentuation of the normal pattern and the development of new zones of thickening. The surfaces about the orifices of the venae cavae, the intervening posterolateral area, and the septal surface, especially over the anterodistal aspect of the limbus of the fossa ovalis, formed a large confluent zone of marked thickening. Nearly as thick were patches on the crista terminalis and on the inferior portion of the anterior wall. Other areas such as the auricular appendage, the pectinate muscle ridges, and the supravalvular zone showed increased thickness compared to controls.

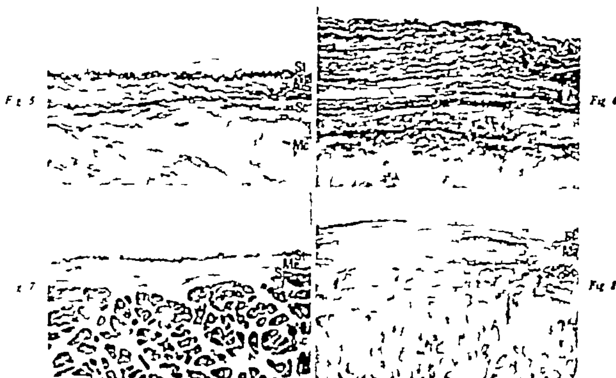
By contrast, the less dilated right atria of the hearts with ASD in the *pressure* group showed far less endocardial thickening than those of the *flow* group. At least one half of the atrial endocardial surface of these hearts remained transparent. In general, increased endocardial thickness in the *pressure* group appeared to be a moderate accentuation of the normal endocardial surface pattern. When focal thickenings were present, these were moderate and occurred in the same sites as in the *flow* group, i.e., at the caval orifices, the crista terminalis, the anterodistal aspect of the limbus of the fossa ovalis, and about the anterior and posterior zones of the coronary sinus.

RIGHT VENTRICLE. The endocardium of the normal right ventricle was very thin only slight thickenings were present in the subvalvular region of the outflow tract and in the posteromedial aspect of the apex. Opacifications reflecting moderate thickening were seen only at the bases of the papillary muscles. In the ASD group with relatively high shunt flow but relatively low pressure right ventricular endocardial thickening was focal but markedly increased as compared to the normals. However endocardial thickening in ASD hearts of the high-pressure, low-shunt group was only slightly greater than normal and was always much less than that seen in hearts of the *flow* group

Four main zones of right ventricular endocardial thickening could be distinguished in the *flow* group (1) just distal to the tricuspid ring over the posterior portions of the septum and free wall (2) approximately midway between the base and apex at the posterior and septal aspects of the sinus region (3) at the apex and the immediately adjacent third of the lateral free wall and (4) in the outflow tract on the septal and parietal aband of the conus arteriosus and in the zone just proximal to the pulmonic valve ring The proximal posterior and septal wall thickenings usually formed distinct plaques extending for about 2 cm from the tricuspid ring These included focal thickenings of the chordae tendineae both at their parietal insertions and in direct apposition to endocardial thickenings particularly large plaques in some specimens appeared to have resulted from coalescence of foci seen as discrete plaques in the same site on other specimens. The midzonal opacifications were thickest and most sharply delimited proximally where free edges of the completely opened tricuspid valve leaflets seemed to abut against the adjacent endocardium other margins were indistinct. These thickenings therefore appeared to be distributed in a circular zone of variable translucency The apical foci were the thickest forming discrete gray white plaques, especially prominent on the luminal aspect of the trabeculae carneae and the papillary muscles the bridging column between the septum and free wall and the bases of the papillary muscles were particularly opacified The outflow tract thickenings were focal and poorly defined most prominent beneath the anterior and right posterior semilunar cusps. Though the distribution of right ventricular endocardial thickenings in the *pressure* group was generally the same as that in the *flow* group the changes were less uniform in the *pressure* group and definite zones were not as easily distinguishable as in the *flow* group

Alterations of endocardial composition and architecture Microscopic examination of the endocardial thickenings in the right atria and ventricles of the hearts with ASD revealed marked departures from normal composition and architecture Two distinct and characteristic patterns of endocardial modification were apparent one in the hearts with relatively high shunt flow but relatively low pressure (*flow* group) and the other in the hearts with relatively high pressure and relatively low shunt flow (*pressure* group) In each group the distinctive features of abnormal endocardial structures were present in both the right atrium and the right ventricle. In Figs. 5 to 8 the microscopic appearance of normal endocardium is compared with that of right atrial and ventricular endocardium in each of the ASD groups. The architecture of the endocardium lining the left atria and ventricles was normal for both groups.

FLOW GROUP In these hearts, endocardial thickening in the *right sided chambers* consisted almost exclusively of fibroelastic proliferation focally in the subendothelial (or superficial) layer and diffusely in the musculoelastic (or medial) layer (Figs. 5 and 6) Increased numbers of subendothelial elastin fibers were aligned parallel to the endocardial surface and in a longitudinal direction (base to apex) with respect to the chamber walls. A fine network of reticulin fibers was distributed among the elastin fibers. In the musculoelastic layer intermingled elastin and collagen fiber were more coarse than in the superficial layer Though also aligned parallel to the endocardial surface fibers in the medial layer were less distinctly oriented with respect to the longitudinal axis of the heart Smooth muscle cells were few and relatively small even in zones such as



F 5 M s pic ppe m right trial end ardi m in normal ad lt The bendothelial layer (SE) m tine la t nd llagen fiber l the musculoela t La er (M) and bet een the subendothelial and m loelas layers fil are th k nd more prominent Smooth m scle cells are parsely scattered and mall The subendocardial la (S adjace t t the my cardium (M) contai fibers nd ery few cells Weigert Gieson t in ×100

Fig 6 Right trial endocardium f heart w th ASD sciated w th gre tly lev ted flow through the defect nd rela iv l low pulmona r artery pressure (flow group) Fibroelastic thickening is marked in both the subendothelial and m sc loelast la ers especially the latter The demarcation bet een the layers is obscured The th k last bers are par llel t the endocardial surface Smooth muscle cells are rare the subendocardial la er is sligh l h k ned (Weigert an Gieson tai ×100)

Fig 7 Right entric lar endocardium of rmal adult heart Although mooth muscle cells nd fibroblasts an be ident fied in he musc loelastic layer these are relativel few and separated by fine elasti nd collagen fibers (Weigert Gieson t in ×100)

Fig 8 Right ventricular endocardi m from heart with ASD sociated th relatively small shu t flow and markedly lev ted pulmonary artery pressure (press re group). I st iking contrast to the normal endocardium (Fig 7), the musculoelastic zone contain prominent bundles of hypertrophied smooth muscle Elastin and collagen fibers are also ncreased, but much less than l heart of the flow group (Fig 6) and largely i the subendothelial nd subendocardial layers.

the posterior aspect of the right atrium where they were abundant in normal hearts. Subendocardial elastin and collagen fibers were normal in appearance and quantity

The greater the fibroelastosis, the less distinct was the demarcation of the endocardial layers. In the right atrium about the caval orifices and the limbus fossae ovalis the subendothelial layer measured up to 150 μ in thickness (approximately 7 times normal) and the musculoelastic layer up to 200 μ (about 4 times normal) the two zones were focally merged (Fig 6) In the posterior portion thickening ranged from 100 to 200 μ (about 3 to 4 times normal) the layers were d stinct. In the distal portions, where thickenings were usually less than twice normal increased fibroelastosis was confined to the discrete subendothelial layer R ght ventricular thickening in both the proximal posterior and outflow tract regions ranged from 100 to 300 μ (5 to 10 times normal) the sharp

demarcation between superficial and medial layers was retained In the middle inflow zone, endocardial thickening was slight and the layers well defined. The apical thickenings varied in degree. Where these were most marked i e. at the tips and bases of the papillary muscles and along the luminal sides of the trabeculae carneae, fibroelastosis was severe attaining thicknesses as great as 650 μ stratification was obliterated subendocardial tissue was focally thickened and fibroelastosis extended into the ventricular wall.

PRESSURE GROUP While the marked endocardial fibroelastosis of the *flow* group was associated with a diminution or absence of smooth muscle the endocardial thickening in the *pressure* group was characterized by striking hypertrophy of smooth muscle cells (Figs. 7 and 8) In the subendothelial layer smooth muscle cells and fibroblasts appeared in groups among increased numbers of elastin and reticulin fibers. The fibers were parallel to the endocardial surface and oriented longitudinally with respect to the chamber walls. In the musculoelastic layer thickening was due largely to smooth muscle hypertrophy with only slight to moderate increase in the associated network of elastin and reticulin fibers the muscle fibers were oriented circumferentially with respect to the chamber walls. Subendocardial tissue was normal. In general thickening of the musculoelastic layer was greater than thickening of the subendothelial layer and stratification was *always* distinct regardless of the degree of endocardial thickening In the right atrium thickening of the musculoelastic layer ranged from 90 to 100 μ (approximately 4 times normal) subendothelial thickening was much more variable, ranging only to twice normal values. In the right ventricle endocardial thickening was almost exclusively muscular with fibrous elements normal or only slightly increased. Fibroelastosis was most prominent over the luminal surfaces of the trabeculae carneae. Smooth muscle hypertrophy in the musculoelastic layer was easily seen in sections of the apex or lateral free wall (Fig. 8)

STAINABLE LIPID ACID MUCOPOLYSACCHARIDE AND METACHROMASIA No extracellular lipid was seen. Occasional cells of the musculoelastic layer contained sudanophilic droplets. The proportion of cells with stainable lipid was not greater than normal in hearts of the *pressure* group no stainable lipid was found in endocardial cells in hearts of the *flow* group Endocardial acid mucopolysaccharide accumulation and metachromasia was most marked in the thickened subendothelial layer of hearts in the *flow* group Scattered foci of moderately increased metachromasia were also seen in the thickened musculoelastic layer of hearts of the *pressure* group

Discussion

The results of the present study indicate that atrial septal defects of the fossa ovalis (secundum) type (ASD) are associated with characteristic patterns of endocardial thickening in the right-sided chambers. Of particular interest is the observation that in ASD associated with relatively high shunt flow and relatively low pulmonary artery pressure endocardial reaction is very marked but exclusively fibroelastic, while in ASD associated with relatively high pressure and relatively low shunt flow endocardial thickening is much less prominent and consists mainly of smooth muscle. The thickening associated with ASD were clearly different from those seen in the normal hearts of the same age the changes were not those of chronic rheumatic endocarditis, for blood vessels were not prominent inflammatory cells were absent and the layers of the endocardium usually remained distinct. Only with extremely marked thickenings in the high-shunt *flow* group were the strata of the endocardium focally merged. The changes differed from atherosclerosis, for stainable lipid could be demonstrated only in a few scattered endocardial cells in the normal and *pressure* groups. Increased interstitial metachromatic or acid mucopolysaccharide accumulation was associated with the relatively acellular fibroelastic thickenings in the *flow* group.

The findings indicate that the composition and structure of the endocardium reflect the functional state of the heart changes associated with increased chamber size without increased pressure are apparently different both quantitatively and

qu ilit itiv ly fr m tl ose ı sociated with increased h her pressures. Although Roesler[24] noted tl it ASD of the fossa v lı t pe w ı ıssociated with endo- ardı l tl ıck n ıg wl ı h wa m st promi nent in tl right ıtrium the a sociation f d t nct pattern f endocardial mpo- tı m w tl pecıfı l modynamic fact rs n ASD l ı not been empl ı ized previ usly

Diffuse f m d gr ss endocardial thick ening has been on dered l y many in vestig tors t be the result of end c rdial d p t tı n t l normal mecl nical tresses nce su l tl ıckening r usually ı soci ted w tl underlying myocardial insuf f ıcıen y and or long st inding hyper t n ıon Dilatation or enlargement of ı rdı l ber presumed to result in a orresp nding ın rease of mur l tension ınd n al norm l stret l ing of the endo- cardıu l l abnormalit es have been attrıl uted t pe sıstent loc ıl di turbances of bl od fl w Endocardial are ıs nor ı ll ul jected to relatively elevated rates f fl l fl w or to turbulent flow or as- s ı t d with relatı ely increased relative t ı n f ıdjacent ır line structures are on dered to be selectively thickened or s ıtıfied during tl e aging process and dur ng the evolution of disease states such end carditıs Several investigators l ıve emphasized that the accumulation of l stin fibers ı a characteristic connec tive tissue response to persistent mecl ani cal strain [21,22] Others have shown that endocardial smooth muscle hypertrophy correlates with cardiac dilatation and hypertrophy ınd elevated systolic pres- sure[4] in cardiac cl ımbers The mecha nisms l y which ıncre ısed cl ımber pressures and volumes result n reconstruction of the endocardium are not cl ır In the present study of hearts with isolated ASD striking differences in endocardial composition cor responded to measured differences in cham ber pressure and shunt flow The associ ated differences ın endocardial tensions and patterns of blood flow therefore merit further discussion

Role of mural tension Consideration of the probable excursions of right ventricular pressures, volumes and mural tensions during the cardiac cycle in normal hearts and in hearts with ASD of the *flow* and *pressure* groups could provide in ight into the n ıture of the corresponding endo- cardial stresses Right ventricular stroke volumes and pulse pressures ol tained from the catheterız ıtion data are compared with normal values in Diagram 2 Average pulse pres ure of the hearts in the *flow* group was nearly normal but was markedly el v ıted in the *pressu e* group l y contrast average stroke volume wa markedly in creased in he ırt of the *flow* group but nearly normal for the heart of the *pressure* group Crude estimates of right ventricular end ystolic and end-dia tolic volume can be made for the heart chambers Formalin fixed ventricles may be presumed to l ave volumes equal to or less than those pres- ent at the end of sy tole[21] right ventricu lar end-systolic volume may therefore be c ılculated using measurements of the tricuspid and pulmonary orifices and the l ngths of the inflow and outflow tracts a described elsewhere The end-dia st lic volume can be con ıdered to be equal to the sum of this calculated end syst lic volume and the corresponding stroke volume ol tained from the cath-

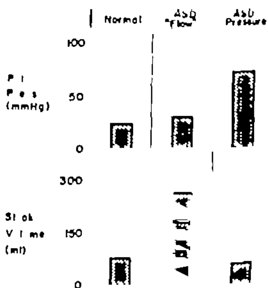


Diagram Comparison o right entricular stroke ol mes and pulse pressures of hearts w th atrial septal defect ith those of normal hearts A erage right entricul pulse pressure of heart in the *flow* group as nearly normal but trok lume was markedly ncreased A erage stroke olume l the *pressu e* group was near normal but pulse pressure as markedly lev ted

eterization data. Approximate radii of curvature corresponding to these end systolic and end-diastolic volumes may be calculated assuming the chambers to be spherical. Corresponding estimates of mural tension at the end of systole and the end of diastole can then be calculated from the expression for the law of Laplace for a spherical surface membrane, $P = \frac{2T}{R}$, where P is the pressure in dynes per square centimeter, R is the radius of curvature in centim ters and T is the tension in dynes per square centimeter. For tension per unit wall thickness, the average right ventricular wall thickness t, in centimeters, can be introduced. The expression for a first approximation of the mural tension per un t wall thickness then becomes $T = \frac{PR}{2t}$, where T is the tension in dynes per square centimeter. Thi value can be considered to represent endocardial tension f it is assumed that the ten sion is distributed uniformly through the wall.

Estimates of maximum and minimum values of right ventricular volume pressure, and endocardial tangential tension during a cardiac cycle are compared for normal ASD-*flow* and ASD-*pressure* groups in Diagram 3. Since heart rates were not elevated in the ASD cases, the durations of the cycles are shown as equal for the three groups: duration of systole and diastole have also been equated for all three. Although change in pressure is greatest in the *pressure* group and change in volume is greatest in the *flow* group, mural tension is elevated n both groups. However, dur ing a cardiac cycle the mural tension may vary less in the *flow* group than in the *pressure* group. In the *flow* group, volume changes appear to balance pressure changes, resulting n a relatively small range of tensions. In the *pressure* group, pressure changes are very marked but corresponding volume changes are small, resulting in great variation in mural tension. The elevated but relatively constant mural tension of the *flow* group was associated with endocardial fibroelastosis. The elevated but rapidl changing mural tension of the *pressure* group was associ

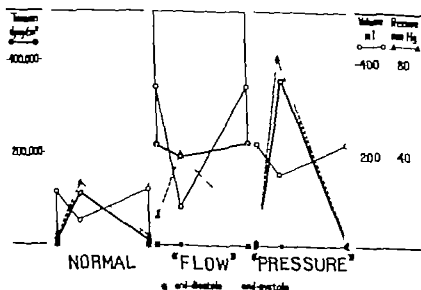


Diagram 3. E timated ranges of chamber olumes, chamber pressures, and mural tensions d ring the cardiac cy le right entricles of normal heart and heart th atrial septal defect. Flow = atrial septal defect associated th markedly ele ted shunt flow and relatively low pulmonary artery pressure. Pressure = atrial septal defect associated th markedly ele ted pulmonary artery pressure nd relatively small shunt flow. The differen ranges of mural tension nd hamber olume are associated with marked differences in endocardial arc hit cture.

ated with smooth muscle hyperplasia and only mild fibroelastosis.

During diastole, when myocardial fibers are relaxed, endocardial stretching should be maximal. The increase in volume during diastole is much greater in the *flow* group than in either the normal or *pressure* groups. Thus, endocardial stretching tension is markedly elevated during diastole in hearts with large shunt flow. Deforming forces in the right ventricles of such hearts are primarily those which tend to stretch or tear the endocardium while the heart wall is relatively passive. If accretion of layers of elastin is indeed a consequence of rhythmic connective tissue stretching, it would be expected to be greater in hearts in the *flow* group. This was indeed the case. In the *pressure* group the greatest increase in mural tension seems to occur during systole, when myocardial fibers are active or contracting; during diastole, when myocardial fibers are relaxed or passive, mural tension falls rapidly. Thus, in the absence of large shunt, deforming forces are primarily those which tend to shorten or compress the endocardium. Smooth muscle proliferation was associated with the presumed increase of endocardial compression. Functionally active endocardial smooth muscle contraction could help to modify deformation of the endocardium, particularly during systole, thereby minimizing shearing effects at the boundary with the contracting myocardium. During diastole, with the myocardium relaxed, shearing effects would probably be relatively insignificant even in the presence of elevated mural tensions.

In the right atrium, endocardial stretching during diastole should be expected to be much greater than normal for the ASD group with high shunt flow and may be nearly normal for the group with relatively low shunt flow. The increased right atrial fibroelastosis in the *flow* group, as compared to the *pressure* group, tends to support the contention that this relatively acellular type of endocardial proliferation is due to passive stretching during diastole. Although right atrial smooth muscle hyperplasia was seen in the right atria of hearts in the *pressure* group, this change was of lesser degree than that observed in the right ventricle. Its occurrence, however, suggests that rate of change of tension may be the major stimulus for endocardial smooth muscle increase, rather than elevated absolute levels of blood pressure or mural tension. Thus, rapid tension change with relatively little diastolic overload would seem to be the combination of factors most closely related to endocardial smooth muscle hypertrophy.

If the distinctive qualitative differences in endocardial composition and architecture between hearts in the *flow* and *pressure* groups are associated with differences in the nature of corresponding endocardial stresses, quantitative differences from site to site are probably due to local differences in mural tension. For a first approximation of the cyclic variations in endocardial tension, as described above, the right ventricle was assumed to be spherical. However, heart chambers are not spherical and effective radii of curvature and wall thicknesses change at different rates in different sites.[11] For example, the configuration of the right ventricular chamber is relatively constant throughout the cardiac cycle in the regions of the valve orifices and about the outflow tract but changes markedly in the regions of the sinus at the lateral free wall and about the apex. Relatively large radii of curvature and relatively thin wall would be associated with relatively high tensions per unit wall thickness. In the right ventricular sinus at the free wall, where endocardial thickening is marked, the myocardium is relatively thin and the mean radius of curvature relatively large. About the caval openings into the right atrium, where endocardial changes are prominent, the effective radius of curvature is comparatively large, for the curvatures of the orifice and of the atrium about the orifice are in opposite directions.

Role of blood flow. Some of the focal subendothelial endocardial thickenings associated with ASD may result from local disturbances of blood flow. The average velocity of blood flow is probably greater in the *flow* group than in the *pressure* group, for the greater stroke volumes of the *flow* group are not associated with corresponding increases in the diameter of the valve orifices. Increased flow rate is associated with decreased lateral pressure

in closed hydrodynamic systems and some authors have considered focally decreased lateral pressure to be a major determinant of the localization of intimal proliferation[24] and atherosclerosis in arterial trees.[17] Focal increases in velocity of blood flow could also result in turbulence depending on the configuration of the chamber at the sites of increase. Although an estimate of Reynolds number for a particular site could conceivably be calculated and shown to be greater than the critical value for laminar flow[11,25] the direct application of Reynolds'[73] observations of the behavior of water in straight cylindrical tubes to the hemodynamic events in the beating heart may be misleading. Nevertheless, the relatively fixed zones about the valve orifices, at the base, about the outflow tract, and about the limbus of the fossa ovalis could conceivably be sites of maximum mean flow rate and minimum mean lateral pressure. Turbulence, if it occurs, could be expected to be maximal where the configuration of the chambers is changing most markedly and rapidly where surfaces are irregular where blood stream currents intersect,[24] converge or separate and where velocity of flow is greatest. Such sites are the midzone of the inflow tract, the apex, the outflow tract the limbus, and the anterior aspect of the coronary sinus. Indeed the endothelial and subendothelial layers of the endocardium showed greater focal selective thickening in the *flow* group than in the *pressure* group at all of these sites.

The diffuse mild endocardial thickenings seen in the left ventricles of hearts with ASD are more readily attributable to deviations from normal blood flow patterns than to changes in mural tension for cyclic variations in pressure and volume are very near normal. Since in ASD the left ventricle receives somewhat less blood than normal from the left atrium its residual volume may be diminished any damping effect on changes in flow rate or departures from laminar flow associated with residual blood would probably be reduced. Furthermore the edge of the septal defect might be expected to intercept the transseptal flow in such a way as to direct a stream of blood toward the posterior commissure of the mitral valve and the posterior portion of the interventricular septum. The corresponding striking changes observed about the mitral valve in hearts with ASD will be discussed in a separate communication

Summary

The nature and distribution of endocardial thickening associated with atrial septal defect of the fossa ovalis (secundum) type (ASD) were studied in seven hearts for which antemortem catheterization data were available. The cases included four with large shunt flow and relatively low pulmonary artery pressure (*flow* group) and three with relatively small shunt flow and high pulmonary artery pressure (*pressure* group) Two distinct and different patterns of endocardial change were evident in the right-sided chambers, one in hearts of the *flow* group the other in those of the *pressure* group. Gross endocardial thickening diffuse in the atrium and focal in the ventricle, was much more marked in the *flow* group In hearts with high shunt flow and relatively low chamber pressure endocardial fibroelastosis was marked and smooth muscle cells were few and atrophic in hearts with small shunt flow but markedly elevated pressure endocardial smooth muscle hyperplasia was a predominant and constant feature. Markedly increased diastolic mural tension and relatively low rates of change of mural tension corresponded to the fibroelastosis in the *flow* group high rates of change of mural tension and increased levels of systolic mural tension corresponded to the smooth muscle hyperplasia in the *pressure* group. Focal superficial (subendothelial) fibroelastosis more marked in the *flow* group, probably corresponded to local increases in velocity of blood flow or turbulence.

REFERENCES

1. Benninghoff A Handbuch mikrosk. Anat. Menschen, Berlin, 1930, Julius Springer IV/1 p 162.
2. Okada, R. Clinicopathological study on the thickening of parietal endocardium in adult heart, Jap. Heart J 2:220, 1961.
3. McMillan, J B and Lev M. The aging heart. I Endocardium, J Gerontol. 14:268, 1959
4. Zahn, F W Über einige anatomische Kennzeichen der Herzklappeninsufficienzen, Verh. Congr. inn. Med. 13:351 1895.

5. Herxheimer, C.: Über Sehnenflecke und Endocardsch..., Beit. path. Anat. 32:161, 1902.
6. Schminck, A.: Endokardiale ... Wien... Virchows Arch. path. Anat. 192:50, 1908.
7. Saphir, O.: Endocardial pocket, Am. J. Path. 6:733, 1930.
8. Saphir, O.: ... evidence of ... disorder of the heart, Arch. Path. 16:315, 1933.
9. Dew..., W.: Über endokardiale Flecken, Frankf. Ztschr. Path. 9:52, 1912.
10. Edwards, J. E., and Burchell, H. B.: Endocardial and intimal lesions (jet impact) as possible sites of origin of murmurs, Circulation 18:946, 1958.
11. Hellerst..., H. K.: Endocardial pocket of left atrium, Am. Heart J. 31:751, 1947.
12. Hertel, M. ...: Verh... des Endokard... Endokard ... und ... allgemeinen Blutdruck... Frankf. Ztschr. Path. 21:1, 1920.
13. Fahr, Virchows Arch. path. Anat. 185:29, 1906.
14. Böger, A.: Über die Endokardsklerosen, Beitr. path. Anat. 81:141, 1928-29.
15. Black-Schaffer, B.: ... endocardial fibroelastosis; a suggested etiology, Arch. Path. 63:281, 1957.
16. Fisher, E. R., and Davis, E. R.: Observations concerning the pathogenesis of endocardial thickening in the adult heart, Am. Heart J. 56:553, 1958.
17. Lev, M., Rowlatt, U. F., and Rimoldi, H. J. A.: Pathologic methods for study of congenitally malformed heart, Arch. Path. 72:493, 1961.
18. Von Glahn, W. C.: Auricular endocarditis of rheumatic origin, Am. J. Path. 2:1, 1926.
19. Gross, M.: Lesions of the left auricle in rheumatic fever, Am. J. Path. 11:711, 1935.
20. Roesler, H.: Interatrial septal defect, Arch. Int. Med. 54:339, 1934.
21. Hass, G. M.: Elastic tissue, Arch. Path. 27:334 and 583, 1939.
22. Miller, A. M., and Perkins, O. C.: Elastic tissue of the heart during aging, Am. J. Path. 3:205, 1927.
23. Eckner, F. A. O., Clagett, S., and Lev, M.: Alterations of cardiac gross morphology by bloat... In preparation.
24. Rowlatt, U. F., Rimoldi, H. J. A., and Lev, M.: The quantitative anatomy of the normal child's heart, Ped. Clin. North America 10:499, 1963.
25. Burton, A. C.: The importance of the shape and size of the heart, Am. Heart J. 54:801, 1957.
26. Rodbard, S.: Vascular modifications induced by flow, Am. Heart J. 51:926, 1956.
27. Texon, M.: The role of vascular dynamics in the development of atherosclerosis, Sandler, M., and Bourne, G. H., editors: Atherosclerosis and its origins, London, 1963, Academic Press, Inc.
28. Kugelmass, I. N.: Biochemistry of blood in health and disease, Springfield, Ill., 1959, Charles C Thomas, Publisher.
29. Ikeda, K.: Potential mechanical factor in vascular dilatation. Wall thickness and vessel growth, Jap. Circulation J. 28:391, 1964.
30. Reynolds, O.: An experimental investigation of the circumstances which determine whether the motion of water shall be direct or sinuous, and of the law of resistance in parallel channels, Phil. Tr. 174:935, 1883.

Experimental and laboratory reports

Temporospatial frequency distribution of P, QRS and T in normal man and woman

J von der Groeben M.D
D D Fisher Ph.D
J G Toole M.D
Palo Alto Calif

This report presents statistical data obtained in a detailed study of normal individuals, each of whom had a three-orthogonal lead electrocardiogram (ECG) recorded on analogue magnetic tape using the Frank lead system

Methods

The ECG amplification system had a linear frequency response of 0 01 cycle to 10 kilocycles. The frequency limiting factor was the analogue tape recorder with a linear response of DC to 1,250 cycles. A normal individual is defined as one in whom no abnormal heart condition was detected by either medical history or physical examination. One heartbeat in a train of 15 to 20 was selected for digitization. An average of 1 2 seconds of data was digitized from each of three leads simultaneously at a rate of 1,000 samples per second. Statistical models of the P wave and the QRS complex (at 1 msec intervals) and T wave (normalized to 60 points in time) were obtained from age groups 15 to 61 years in rectangular polar coordinates, and ellipsoidal (F test) coordinates. This report will be confined to the presentation of polar coordinate data of age groups 20 30 40 and 50 with a total of 455 individuals.

The display of the instantaneous dipole vector as a function of time combines the advantage of vector representation with the advantage of time display as used in the scalar ECG The instantaneous vector is given by its spherical coordinates, which consist of two angles and the spatial magnitude (Fig 1) This representation allows an immediate insight into the cardiac vector position at a given moment

In order to utilize the experience and tradition of electrocardiography we describe the vector in terms of Einthoven's angle and its tilt which is the angle between the heart vector and the frontal plane Projecting a terrestial sphere into the center of the chest (Fig 1) this means that if the pole axis is made to coincide with the anatomical anterior posterior axis and the equatorial plane to coincide with the frontal plane corresponds to longitude and tilt corresponds to latitude. Spatial magnitude is the absolute magnitude as opposed to the magnitude of a vector loop projection which is dependent on the plane of projection The frequency distribution of the QRS com-

This study was supported by grants from the United States Public Health Service National Heart Institute (HE 073 3-02 and HE 08203-01) and National Science Foundation Grant GP-449.
Received for publication May 1967
*Stanford University School of Medicine Palo Alto, Calif

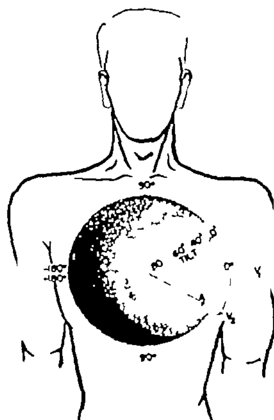


Fig. 1. A sphere projected into the torso. Any point on the sphere is defined by two angles, here α and tilt. ... represent ... ect with α = 0 and tilt = 0°. ... vector with α = +30° and ... back, and tilt of +50° ... penetrates the posterior hemisphere at point A. Tilt values are negative when on anterior hemisphere and positive when on posterior hemisphere.

plex in normal individuals was previously demonstrated.[3] This normal distribution range was then used as a background against which abnormal individuals were studied.[4] The normal range served as a guide to determine abnormalities. The coordinate system functions in this case as an enveloping surface for a given instant of time. The number of points outside the normal range was counted for the normal and the abnormal population and the 95 per cent range was used as the separation line which means that the criteria were made such that only 5 per cent of the normal population would be outside the enveloping surface. The smallness of the sample size of the first normal study[4] and its limitation to the QRS complex was a definite shortcoming. For this reason the following study was undertaken which comprises normal individuals between the ages of 15 and 61 in which one complete cardiac cycle from the beginning of P to the end of T was analyzed at 1 msec. intervals for each individual. All individuals were studied in the Frank lead system and Helm modification of Frank lead system. This report will be confined to the data of the Frank system.

Analogue-to-digital conversion. Four channels of the analogue source tape were used in this study, three as data channels (X, Y, and Z) and the fourth to supply a two-state trigger signal for the analogue-to-digital converter signals. Signals on the three data channels were converted to digital form only when the associated trigger channel was at the one-volt level. The duration of the visually placed trigger signal was not less than one heartbeat. A trigger signal was also recorded on a part of the associated calibration signal so that both selected parts of cardiogram and calibration curves were digitized. The ADC system used had Texas Instruments DC voltmeters, and buffers with support electronics by Lockheed Missile and Space Company. A CEC tape recorder driven at 15 inches per second served as the input source to the ADC. Each of the three data tracks was sampled at 1,000 samples per second with a 25 microsecond delay from track to track of a triple. Each converted value had a resolution of 1 part in ,047. The digital output was written on 7090-IV compatible tape at a density of 200 characters per inch in a buffered mode so that no data were lost when the record gaps were written. Each lead of an ECG was scaled by its associated calibration value on an IBM 7090 and a tape was prepared for a Cal Comp incremental plotter. Each ECG was plotted (with appropriate label and axis) on a scale of 18 inches for each second of data on the horizontal axis and of 2.5 inches per millivolt on the vertical scale. Several types of smoothing were investigated. In this study it was decided to use a 7 point linear moving window smoothing for the plots (the ECG's were retained in their unsmoothed form for statistical calculations). The plotted cardiograms were used for onset determination and as a permanent record for the patient's file.

Statistics were gathered by sex and age at one-year increments for ages 15 to 61 for P and QRS at 1 msec. intervals and for the T wave normalized to 60 equal parts of time. The information for age groups up to four years younger and four years older was combined to give the tables presented in this report. The statistics for age 20, for instance, consist of values from ages 16 to 24.

Programs were written for the IBM 7090 in Subalgol, a Stanford University version of Algol for the 7090. Several programs were required for the data editing and reduction portion of the study. Tables at 1 msec. intervals for each P and QRS and at 1/60 of the time normalized T wave as well as condensed tables at 5 msec. intervals for P and QRS and 1/30 of the time normalized T wave in both rectangular and spherical coordinates for 43 age groups were printed. The age groups 20, 30, 40, and 50 of P, QRS, and T in polar coordinates were selected for this report. Values for P and QRS are presented at 5 msec. intervals. The time normalized values of the ST-T segment are presented in 1/30 of total ST-T time.

Fig. 1 depicts the coordinate system which was adopted in this study. Let $x = \overline{OA}$, $y = \overline{AB}$ and $z = \overline{BC}$. Traditional polar angles in degrees are defined in Equation 1 at bottom of page.

With these definitions α has the range $-180° < \alpha \leq 180°$ and tilt has the range $-90° \leq t \leq 90°$. Thus the angle α has a discontinuity along the negative x-axis with a jump of 360° as one goes from positive y values to negative y values. The definition of α requires that the mean be computed before the standard deviation σ_α can be computed. This requires two complete passes of the input data.

In order that individuals with large spatial magnitudes do not have a disproportionate effect on the mean angles $\bar{\alpha}$ and $\bar{t}$, these means are computed from unit vectors as follows. Let $u = \Sigma (x_i/r_i)$, $v = \Sigma (y_i/r_i)$ and $w = \Sigma (z_i/r_i)$; then the spherical mean values are defined by

$$(2)\quad \begin{cases} \bar{t} = \dfrac{180}{\pi} \arcsin(w/p) \\ \bar{\alpha} \begin{cases} \dfrac{-180}{\pi} \arctan(v/u) \\ \quad u > 0,\ v \neq 0 \\ \quad \text{etc.} \end{cases} \end{cases}$$

where $p = \sqrt{u^2 + v^2 + w^2}$

Standard deviations for all coordinates have textbook definitions except σ_α, which for a given point in time has the definition

$$(3)\ \sigma_\alpha = \sqrt{(\Sigma_k (\zeta_k)^2)/N}$$

where

$$(4)\ \zeta = \begin{cases} 360 - |\alpha - \bar{\alpha}|, & |\alpha - \bar{\alpha}| > 180 \\ \alpha - \bar{\alpha} & \text{otherwise.} \end{cases}$$

The Cartesian zero point, i.e., the spatial reference zero point for each wave component was selected as follows:

Zero reference for P wave = onset of P

$$(1)\quad \begin{cases} r = \sqrt{x^2 + y^2 + z^2} \\ t = \dfrac{180}{\pi} \arcsin(z/r) \\ \alpha = \begin{cases} 0 & x > 0,\ y = 0 \\ 180 & x < 0,\ y = 0 \\ -90\ \text{sgn}(y) & x = 0,\ y \neq 0 \\ \dfrac{-180}{\pi} \arctan(y/x) & x > 0,\ y \neq 0 \\ -\left[180 - \dfrac{180}{\pi} \arctan(y/x)\right]\ \text{sgn}(y) & x < 0,\ y \neq 0 \end{cases} \end{cases}$$

Zero reference for QRS = onset of QRS
Zero reference for ST-T segment = onset of P

There is generally a considerable difference between the zero reference onset of P and QRS which is given by the magnitude of the Ta wave vector. It was assumed that in normal individuals most of the Ta wave vector has vanished at the time of the ST segment. The zero reference for the ST segment can therefore be considered equal to the onset of P. If the onset

Fig. 21. Mean and two standard deviation values of the P wave plotted by the incremental plotter (the plotter served as an output device to the computer system); [illegible] 20 Frank lead system. Time values are given at 5 msec. intervals.

technique is not observed or if the junction point between QRS and T was selected as zero reference point for the ST T segment important ST segment changes could be overlooked in the spherical angle display

Results

P wave. The spatial magnitude of P shows a smooth curve with peak values between 50 and 60 msec. (see Figs. *2A* *2B* *2C* and *2D* see also Tables I II III and IV) There are no essential differences

Fig. 2B Mean and two standard deviation values of the P wave as plotted by the incremental plotter age 30- Frank lead system

between the male and female individuals. The mean α value of P shows a characteristic downward trend, the equivalent of a counterclockwise rotation in the frontal plane. This is observed in all age groups and in both sexes. The mean tilt value of P shows anterior values for the initial 50 msec. and posterior values for the terminal 50 msec. This also seems to be characteristic for both sexes throughout all age groups.

The standard deviation values of P

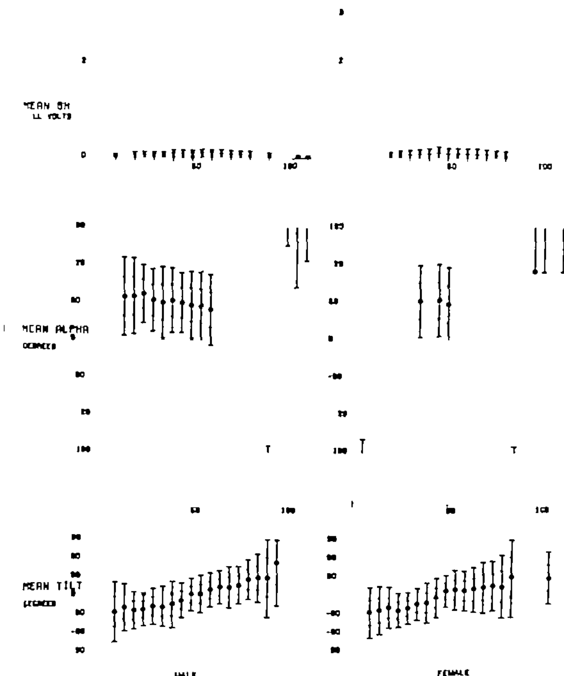


Fig. 2C. Mean and two standard deviation values of the P wave as plotted by the incremental plotter; age 40, Frank lead system.

appear larger than we would clinically expect, particularly in α This is due to the unfavorable signal to noise ratio which exists in the low voltage range of the P wave.

QRS wave

SPATIAL MAGNITUDE (SM) All male groups show a larger spatial magnitude peak than the respective female groups (see Figs. 3A 3B 3C and 3D) There is a decrease of spatial magnitude with age, primarily in the period from 35 msec. to the termination of QRS in men but symmetrically throughout the duration of the QRS in

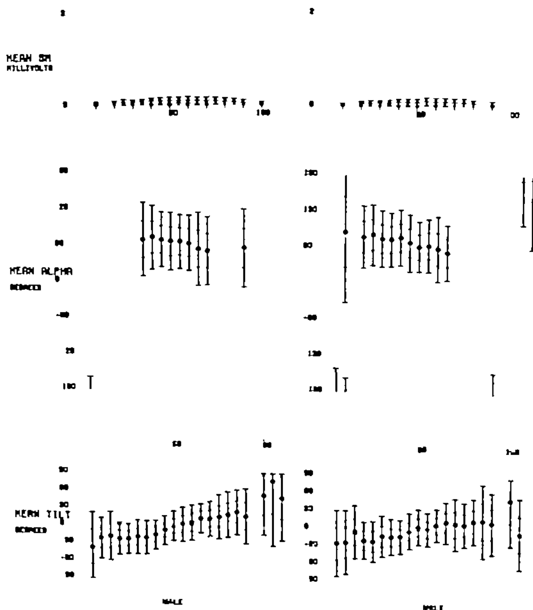


Fig 2D Mean and two standard deviation values of the P wave as plotted by the incremental plotter age 50 Frank lead system

Table I Means and standard deviations, age 20

Spatial magnitude (mV)		α (degrees)		Tilt (degrees)		Number		Time (msec)
M	F	M	F	M	F	M	F	
P wave								
0.07(0.03)	0.07(0.03)	77(32)	74(45)	−22(18)	−19(17)	78	91	20
0.12(0.04)	0.11(0.04)	75(22)	69(37)	−16(10)	−12(15)	77	91	40
0.12(0.06)	0.10(0.05)	59(31)	59(33)	1(14)	4(18)	77	91	60
0.06(0.03)	0.05(0.03)	39(52)	35(65)	17(17)	20(27)	72	86	80
0.04(0.02)	0.01(0.01)	−31(77)	−79(87)	45(40)	19(33)	35	34	100
QRS wave								
0.03(0.0[illegible])	0.01(0.02)	−125(74)	−110(78)	−60(47)	−63(37)	78	91	5
0.13(0.05)	0.12(0.05)	−121(58)	−113(56)	−60(20)	−59(20)	78	91	10
0.[illegible]5(0.10)	0.24(0.11)	−123(70)	−109(74)	−69(18)	−69(19)	78	91	15
0.36(0.13)	0.34(0.15)	−81(90)	−31(85)	−83(23)	−82(25)	78	91	20
0.50(0.17)	0.46(0.20)	24(78)	29(59)	−70(18)	−59(22)	78	91	25
0.7[illegible](0.27)	0.68(0.28)	36(27)	41(20)	−42(21)	−26(22)	78	91	30
1.11(0.36)	1.09(0.38)	41(11)	47(11)	−16(16)	−3(17)	78	91	35
1.60(0.4[illegible])	1.48(0.43)	45(9)	52(10)	0(11)	10(15)	78	91	40
1.91(0.49)	1.64(0.53)	48(12)	55(16)	12(15)	20(17)	78	91	45
1.81(0.55)	1.45(0.59)	50(33)	59(36)	24(22)	35(21)	78	91	50
1.52(0.51)	1.13(0.54)	57(53)	71(61)	41(25)	53(23)	78	91	55
1.16(0.49)	0.80(0.43)	80(66)	95(69)	62(25)	69(25)	78	91	60
0.83(0.41)	0.51(0.31)	170(70)	142(72)	73(23)	76(25)	78	91	65
0.59(0.35)	0.36(0.23)	164(71)	162(76)	76(25)	78(35)	78	91	70
0.40(0.[illegible]2)	0.23(0.18)	−168(75)	157(75)	77(36)	75(41)	78	90	75
0.27(0.17)	0.17(0.14)	−149(87)	144(80)	76(52)	69(52)	75	74	80
0.19(0.13)	0.13(0.10)	−118(92)	145(77)	67(53)	57(49)	62	54	85
0.14(0.10)	0.11(0.08)	−81(91)	125(78)	68(61)	30(40)	49	34	90
T wave								
0.09(0.03)	0.06(0.03)	32(74)	78(102)	−70(32)	−86(59)	78	91	1
0.11(0.04)	0.07(0.03)	27(65)	1(97)	−67(22)	−81(50)	78	91	2
0.13(0.04)	0.07(0.03)	29(48)	6(77)	−62(20)	−68(38)	78	91	3
0.15(0.05)	0.08(0.03)	27(43)	26(71)	−57(17)	−58(31)	78	91	4
0.18(0.06)	0.09(0.04)	35(36)	23(54)	−55(15)	−48(25)	78	91	5
0.22(0.07)	0.11(0.05)	33(27)	26(44)	−48(15)	−40(21)	78	91	6
0.28(0.09)	0.15(0.06)	36(20)	29(37)	−45(15)	−33(18)	78	91	7
0.36(0.12)	0.20(0.09)	35(17)	32(25)	−41(15)	−23(17)	78	91	8
0.45(0.15)	0.29(0.11)	35(15)	34(21)	−37(15)	−17(15)	78	91	9
0.53(0.18)	0.36(0.13)	37(13)	37(19)	−32(15)	−12(14)	78	91	10
0.55(0.19)	0.40(0.13)	40(13)	39(16)	−26(15)	−8(13)	78	91	11
0.45(0.15)	0.36(0.12)	43(13)	43(15)	−22(13)	−7(13)	78	91	12
0.25(0.09)	0.22(0.08)	48(15)	47(20)	−23(13)	−12(15)	78	91	13
0.11(0.04)	0.11(0.04)	53(30)	53(42)	−30(17)	−19(21)	78	91	14
0.06(0.03)	0.06(0.03)	68(78)	61(73)	−54(39)	−36(36)	78	91	15

SD values are given in parentheses. The number of individuals decreases toward the end of P and QRS as the [illegible] complexes [illegible] earlier in some individuals than in others. The ST-T segment values are given at 1/15 of [illegible] length of this segment. The arrangement of values and symbols [illegible] the same for Tables II, III, and IV.

Table II. Means and standard deviations age 30

Spatial magnitude (mV.)		α (degrees)		Tilt (degrees)		Number		Time (msec.)
M	F	M	F	M	F	M	F	
P wave								
0.07(0.03)	0.07(0.03)	81(40)	80(38)	−28(19)	−16(17)	41	34	20
0.11(0.04)	0.11(0.04)	78(36)	76(34)	−13(12)	−13(11)	41	34	40
0.12(0.05)	0.11(0.05)	65(30)	60(37)	7(11)	2(19)	41	34	60
0.08(0.04)	0.05(0.03)	46(42)	44(57)	22(22)	20(27)	41	33	80
0.04(0.03)	0.02(0.01)	−11(97)	−42(91)	70(56)	39(47)	29	7	100
QRS wave								
0.04(0.02)	0.03(0.02)	−132(60)	−127(66)	−55(34)	−51(40)	41	34	5
0.12(0.06)	0.11(0.05)	−142(49)	−119(76)	−58(18)	−67(32)	41	34	10
0.22(0.10)	0.18(0.07)	−133(53)	−115(95)	−63(19)	−83(33)	41	34	15
0.31(0.14)	0.26(0.09)	−108(87)	17(79)	−79(24)	−73(24)	41	34	20
0.42(0.17)	0.41(0.15)	7(84)	23(45)	−72(21)	−45(23)	41	34	25
0.62(0.24)	0.65(0.25)	26(42)	31(15)	−44(22)	−20(20)	41	34	30
0.93(0.32)	1.00(0.32)	34(28)	38(10)	−20(18)	−1(15)	41	34	35
1.32(0.40)	1.28(0.36)	40(14)	43(11)	−3(16)	10(13)	41	34	40
1.54(0.49)	1.32(0.44)	44(16)	44(19)	9(14)	20(18)	41	34	45
1.50(0.60)	1.11(0.44)	48(19)	48(50)	22(19)	37(21)	41	34	50
1.30(0.48)	0.81(0.29)	59(41)	60(72)	40(25)	59(24)	41	34	55
1.00(0.36)	0.61(0.23)	74(50)	108(82)	55(23)	75(28)	41	34	60
0.73(0.29)	0.44(0.20)	107(62)	171(70)	67(20)	77(29)	41	34	65
0.55(0.25)	0.29(0.16)	141(38)	−157(68)	70(20)	71(31)	41	34	70
0.40(0.23)	0.20(0.11)	152(67)	−136(76)	69(27)	62(38)	41	32	75
0.29(0.19)	0.15(0.09)	158(73)	−132(80)	66(33)	52(45)	40	28	80
0.21(0.16)	0.12(0.07)	139(86)	−112(70)	66(45)	21(26)	38	20	85
0.15(0.13)	0.08(0.04)	143(95)	−143(65)	42(51)	5(31)	32	15	90
T wave								
0.08(0.03)	0.07(0.02)	−64(103)	−117(60)	−86(39)	−36(30)	41	34	1
0.10(0.03)	0.07(0.02)	−12(92)	−124(66)	−81(29)	−50(34)	41	34	2
0.11(0.04)	0.06(0.02)	14(74)	−100(83)	−73(25)	−64(34)	41	34	3
0.13(0.04)	0.07(0.03)	14(65)	−101(91)	−69(22)	−71(40)	41	34	4
0.18(0.05)	0.07(0.03)	21(46)	−45(82)	−61(16)	−70(38)	41	34	5
0.19(0.06)	0.08(0.04)	28(32)	−1(73)	−55(15)	−67(33)	41	34	6
0.24(0.08)	0.10(0.05)	31(24)	7(65)	−51(14)	−52(30)	41	34	7
0.31(0.10)	0.14(0.07)	35(21)	23(42)	−46(14)	−34(28)	41	34	8
0.40(0.12)	0.20(0.09)	37(18)	34(43)	−40(13)	−28(24)	41	34	9
0.47(0.14)	0.27(0.13)	39(17)	38(31)	−35(13)	−18(20)	41	34	10
0.48(0.14)	0.31(0.13)	42(16)	42(32)	−30(12)	−12(18)	41	34	11
0.38(0.12)	0.30(0.12)	46(14)	46(27)	−26(11)	−11(16)	41	34	12
0.22(0.08)	0.20(0.08)	51(17)	50(19)	−25(11)	−17(11)	41	34	13
0.11(0.05)	0.10(0.04)	57(33)	60(37)	−30(14)	−25(23)	41	34	14
0.07(0.05)	0.06(0.0[illegible])	62(74)	84(81)	−56(31)	−55(37)	41	34	15

See note below Table I.

Table III Means and standard deviations age 40

Spatial magnitude (mv)		α (degree)		Tilt (degrees)		Number		Time (msec.)
M	F	M	F	M	F	M	F	
P wave								
0 07(0 03)	0 07(0 03)	72(30)	70(37)	−23(15)	−17(17)	58	54	20
0 11(0 03)	0 11(0 05)	65(26)	65(37)	−14(19)	−10(16)	58	54	40
0 11(0 03)	0 11(0 06)	48(28)	51(31)	8(14)	8(16)	58	54	60
0 07(0 03)	0 06(0 05)	25(42)	49(59)	26(16)	14(25)	57	51	80
0 01(0 02)	0 01(0 03)	−45(81)	−91(78)	41(44)	28(45)	40	25	100
QRS wave								
0 01(0 02)	0 03(0 02)	−140(75)	−117(80)	−6 (33)	−58(39)	58	56	5
0 11(0 05)	0 11(0 05)	−146(62)	−133(63)	−65(24)	−67(21)	58	56	10
0 20(0 12)	0 21(0 08)	−127(76)	−107(82)	−72(4)	−77(24)	58	56	15
0 27(0 15)	0 29(0 10)	−43(96)	7(83)	−83(28)	−75(27)	58	56	20
0 40(0 18)	0 43(0 19)	14(67)	27(49)	−60(20)	−47(25)	58	56	25
0 61(0 28)	0 71(0 [illegible]9)	23(30)	32(17)	−32(19)	−17(20)	58	56	30
1 00(0 36)	1 09(0 37)	29(24)	37(13)	−13(16)	1(15)	58	56	35
1 34(0 39	1 33(0 39)	32(21)	41(13)	−3(17)	12(15)	58	56	40
1 47(0 44	1 34(0 43)	35(15)	45(23)	6(16)	24(17)	58	56	45
1 [illegible]1(0 51)	1 16(0 47)	37(22)	53(44)	19(19)	39(21)	58	56	50
1 07(0 48)	0 88(0 40)	47(50)	69(66)	40(25)	58(23)	58	56	55
0 86(0 40)	0 62(0 30)	69(63)	101(73)	60([illegible]6)	72(24)	58	56	60
0 69(0 35)	0 42(0 22)	110(61)	146(78)	71(26)	75(24)	58	56	65
0 50(0 29)	0 28(0 17)	144(78)	173(79)	77(31)	75(32)	58	56	70
0 35(0 2)	0 19(0 12)	162(81)	−175(75)	76(37)	68(39)	57	51	75
0 25(0 16)	0 13(0 09)	143(85)	−162(77)	78(44)	59(45)	54	45	80
0 18(0 12)	0 10(0 07)	130(90)	−173(84)	76(51)	53(47)	49	33	85
0 13(0 10)	0 09(0 01)	110(99)	179(67)	49(42)	31(35)	39	17	90
T wave								
0 08(0 03)	0 06(0 03)	−85(107)	−144(78)	−86(42)	−55(39)	58	56	1
0 09(0 03)	0 07(0 03)	−28(85)	−143(88)	−79(31)	−69(38)	58	56	2
0 11(0 04)	0 07(0 03)	−1(79)	−103(100)	−70(27)	−80(45)	58	56	3
0 12(0 04)	0 07(0 03)	11(64)	6(89)	−66(21)	−83(43)	58	56	4
0 14(0 05)	0 08(0 04)	14(60)	22(79)	−63(19)	−70(33)	58	56	5
0 18(0 07)	0 10(0 04)	23(55)	29(67)	−56(17)	−55(25)	58	56	6
0 23(0 10)	0 13(0 06)	25(30)	29(49)	−51(18)	−44(20)	58	56	7
0 30(0 12)	0 18(0 08)	29(22)	31(33)	−46(15)	−34(17)	58	56	8
0 39(0 14)	0 26(0 11)	31(18)	30(25)	−41(13)	−26(16)	58	56	9
0 46(0 15)	0 33(0 12)	33(16)	34(16)	−37(13)	−20(14)	58	56	10
0 48(0 14)	0 37(0 12)	36(15)	37(15)	−33(13)	−17(12)	58	56	11
0 38(0 11)	0 33(0 10)	39(14)	41(16)	−29(12)	−17(12)	58	56	12
0 22(0 06)	0 21(0 06)	45(19)	51(28)	−29(13)	−20(15)	58	56	13
0 10(0 04)	0 11(0 03)	50(38)	59(42)	−35(19)	−22(19)	58	56	14
0 06(0 03)	0 07(0 03)	50(67)	73(68)	−48(34)	−32(31)	58	56	15

See note below Table I.

Table IV. Means and standard deviations, age 50

Spatial magnitude (mV)		α (degrees)		Tilt (degrees)		Number		Time (msec)
M	F	M	F	M	F	M	F	
P wave								
0.07(0.02)	0.07(0.03)	81(41)	79(26)	−23(13)	−19(16)	49	45	20
0.11(0.03)	0.11(0.03)	73(26)	79(23)	−16(12)	−11(14)	49	45	40
0.12(0.04)	0.11(0.04)	65(23)	59(27)	5(15)	9(14)	49	45	60
0.09(0.04)	0.07(0.04)	48(33)	40(53)	19(19)	17(19)	49	43	80
0.04(0.02)	0.04(0.02)	6(74)	−35(73)	53(33)	54(39)	38	29	100
QRS wave								
0.03(0.01)	0.04(0.02)	−136(79)	−118(83)	−68(36)	−69(43)	49	47	5
0.10(0.05)	0.12(0.05)	−160(62)	−130(71)	−65(26)	−67(25)	49	47	10
0.18(0.08)	0.22(0.09)	−169(73)	−125(77)	−75(23)	−74(26)	49	47	15
0.27(0.12)	0.27(0.11)	15(105)	−19(88)	−84(28)	−81(25)	49	47	20
0.43(0.19)	0.38(0.16)	18(61)	22(37)	−59(20)	−47(21)	49	47	25
0.68(0.31)	0.63(0.20)	20(19)	32(15)	−35(17)	−13(20)	49	47	30
1.03(0.37)	0.99(0.24)	24(14)	37(13)	−16(12)	3(18)	49	47	35
1.30(0.38)	1.27(0.31)	28(15)	41(14)	−5(13)	13(17)	49	47	40
1.35(0.41)	1.33(0.38)	33(21)	45(30)	8(16)	24(17)	49	47	45
1.20(0.45)	1.14(0.41)	36(43)	49(36)	26(20)	39(21)	49	47	50
0.98(0.40)	0.88(0.33)	46(60)	57(57)	50(22)	57(25)	49	47	55
0.83(0.32)	0.64(0.29)	81(80)	81(78)	72(23)	74(29)	49	47	60
0.66(0.26)	0.44(0.25)	128(89)	133(87)	80(26)	81(29)	49	47	65
0.47(0.21)	0.30(0.21)	170(81)	173(91)	79(25)	77(34)	49	47	70
0.33(0.17)	0.21(0.18)	180(73)	163(88)	76(33)	70(46)	49	44	75
0.22(0.14)	0.16(0.16)	169(78)	175(85)	72(37)	68(50)	47	35	80
0.15(0.10)	0.12(0.14)	132(87)	174(89)	76(49)	58(53)	42	27	85
0.11(0.07)	0.11(0.14)	155(82)	−178(90)	41(45)	−10(56)	31	13	90
T wave								
0.07(0.03)	0.06(0.03)	−162(101)	−137(86)	−80(50)	−59(39)	49	47	1
0.08(0.03)	0.07(0.03)	142(95)	−130(84)	−89(42)	−70(36)	49	47	2
0.09(0.04)	0.07(0.03)	41(88)	−140(102)	−80(38)	−82(43)	49	47	3
0.10(0.05)	0.07(0.03)	16(76)	−8(89)	−69(28)	−79(44)	49	47	4
0.14(0.05)	0.08(0.03)	25(60)	16(77)	−62(23)	−74(39)	49	47	5
0.16(0.07)	0.09(0.04)	30(39)	22(66)	−57(22)	−61(37)	49	4	6
0.21(0.09)	0.12(0.05)	33(38)	32(44)	−53(20)	−47(25)	49	47	7
0.28(0.12)	0.17(0.07)	34(26)	32(39)	−47(19)	−40(22)	49	47	8
0.36(0.15)	0.24(0.10)	36(18)	35(23)	−43(17)	−30(19)	49	47	9
0.43(0.16)	0.32(0.12)	37(17)	35(21)	−38(17)	−22(17)	49	47	10
0.44(0.16)	0.36(0.13)	38(19)	40(18)	−34(15)	−18(18)	49	47	11
0.36(0.13)	0.34(0.13)	42(19)	42(16)	−31(16)	−16(14)	49	47	12
0.21(0.08)	0.22(0.09)	46(29)	49(24)	−28(15)	−18(10)	49	47	13
0.11(0.04)	0.11(0.04)	57(45)	61(39)	−25(25)	−23(17)	49	47	14
0.07(0.03)	0.06(0.03)	74(74)	78(60)	−38(37)	−27(31)	49	47	15

See note below Table I.

women. In the female groups the ascending limb of the SM curve between 25 and 40 msec. has approximately equal values with the corresponding male values, whereas the descending limb of the curve between 40 and 0 msec. shows markedly larger values in the male than in the female group.

ALPHA. The scatter is large during the first 25 msec. but there is through all age groups a noticeable gap of vector points during the first 15 msec. This gap extends

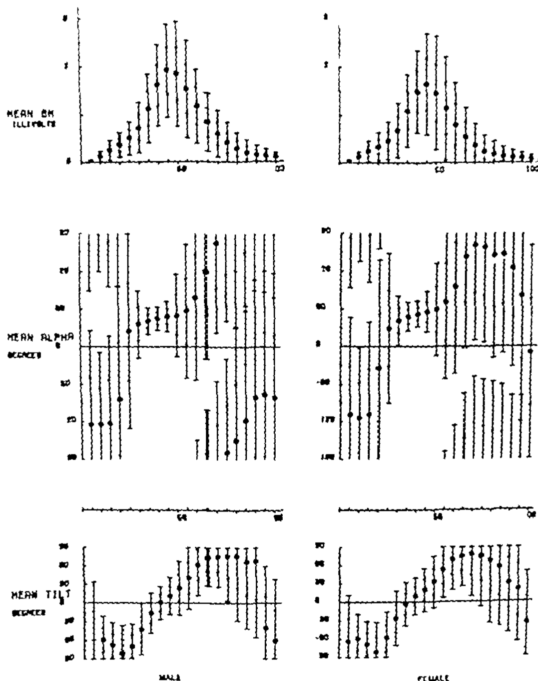


Fig. 31. Mean and 1 standard deviation values of the QRS complex; age 20. Frank lead system. Time values are given at 5 msec. intervals.

from 0° to +130° in the younger individuals and becomes smaller with age. In the male groups, this window also moves to the left with age. The Q waves normally observed in Leads I, II, and III as well as AVF are the corresponding feature of the standard ECG. The scatter of α is characteristically narrow between 30 and 50 msec, reaching a minimum between 40 and 45 msec. in all male and female groups. The scatter during this time interval increases with age in the male but not in

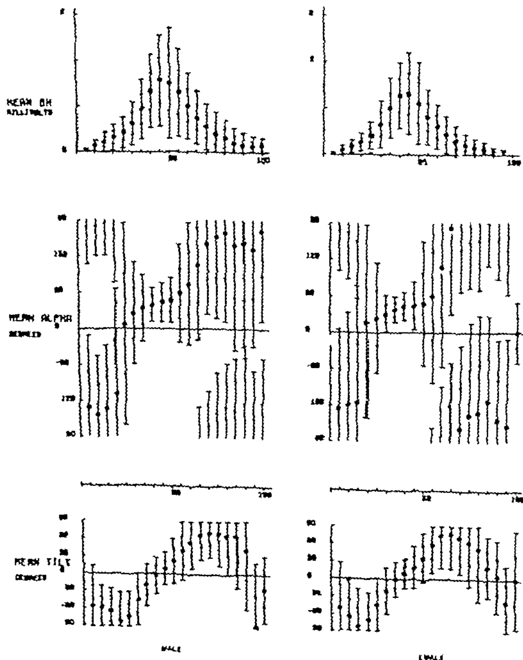


Fig. 38. Mean and standard deviation values of the QRS complex, age 30; Frank lead system.

nificantly in the female group All male groups demonstrate a slightly more leftward orientation at the time of the SM peak except for age group 30 in which both sexes show the same direction of α at the SM peak time

Tilt. The general scatter of tilt is more uniform than the scatter of α. Minimal scatter occurs between 35 and 45 msec. The mean values between 35 and 45 msec. show a more backward tilt in the female than in the male groups but then the male group is tilted more posteriorly during the period from 70 to 90 msec. No tilt

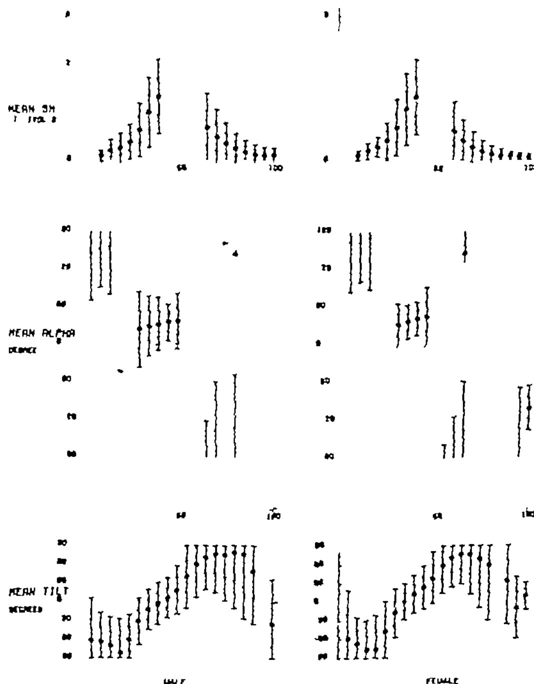


Fig. 3C. Mean and two standard deviation values of the QRS complex age 40; Frank lead system

changes are observed with progressing age.

T wave. The ST T segment was divided into 60 equal parts (see Figs. 4A 4B 4C and 4D) A time normalization was essential since the duration of this segment which constitutes repolarization is heart rate dependent. Tables I to IV give 1/15 of total ST T segment value. Figs. ? to 5 show values of 1/30 of total ST T segment time.

SPATIAL MAGNITUDE. The spatial magnitudes of all male groups show larger values than the corresponding female groups.

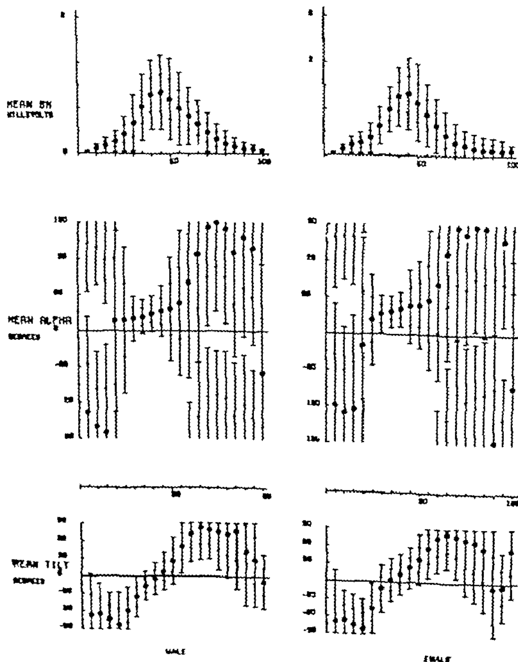


Fig. 3D Mean and standard deviation values of the QRS complex; age 50 Frank lead system.

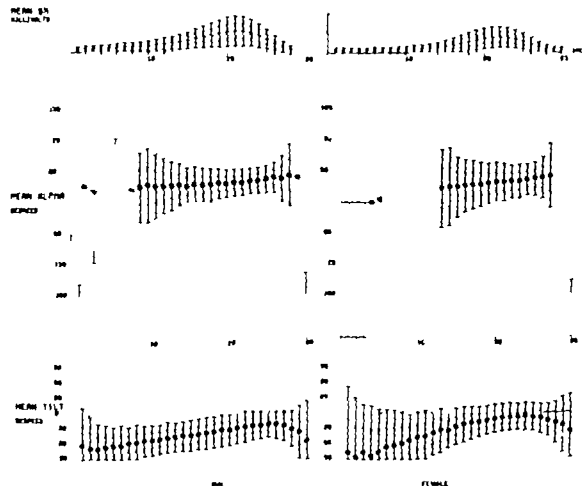


Fig. 4. Time-normalized values of the ST-T segment, means and two standard deviations plotted at 1/30 of total ST-T segment length, age 20. Frank lead system.

There is an earlier rise in the male than in the female and a later fall in the female than in the male groups. There is also a decrease in magnitude with increasing age in both sexes.

ALPHA. There are no noticeable differences in the distribution of α values either between age groups or sexes.

TILT. Characteristic differences between men and women are seen in the configuration of the distribution of tilt. Figs. 2C and 3C show this clearly. The male groups of ages 20 and 30 show an earlier onset of posterior tilting than the respective female groups, but at the time of maximal SV values the female groups show a more posterior tilting than the male. There is an increasing anterior tilt with age in male and female groups. The mean value of anterior tilting of the female age 50 group is still less anterior than the mean anterior tilting of the male age 20 group. The tilt values represent the most noticeable differences between the male and female groups and between age groups.

Discussion

The principal limitations of this study are twofold: (1) the fixed location equivalent dipole representation is only a first

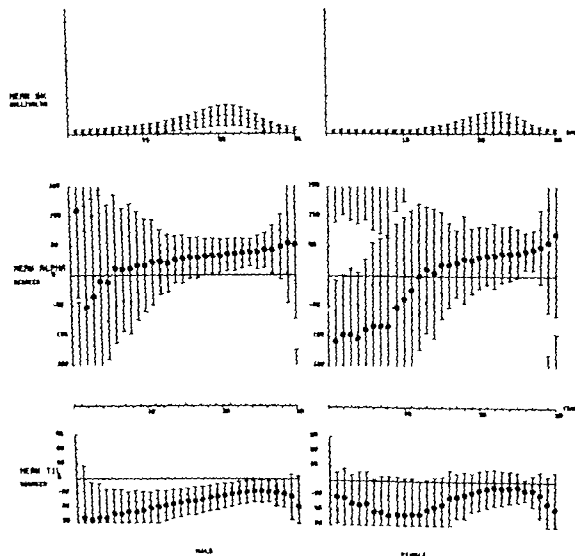


Fig. 4B. Time-normalized values of the ST-T segment mean, and two standard deviation values plotted at 1/30 of total ST-T segment length. Age 30. Frank lead system.

approximation of the cardiac signal generator, and (3) the probability density functions presented here as time functions of the spherical coordinates are also only an approximation in the sense that better fitting statistical envelopes can be obtained around the actual instantaneous spatial clusters. The fact that nondipolar elements have an unfavorable signal-to-noise ratio and that a greater number of leads are required to obtain this information makes a multipole analysis considerably more difficult in clinical applications. One may expect that a detailed thorax mapping will in some instances reveal additional information. Statistical data of this method for age groups and for both sexes are not available at this time.

The limitations of the probability density functions of such spherical coordinates have been discussed elsewhere. The advantage of this method is its direct applicability to the physiologic model. The use of alpha and tilt rather than of azimuth and elevation allows a direct read-out of the instantaneous heart axis as projected into the frontal plane. It is this axis which has been referred to in most ECG investigations concerning acquired and congenital heart disease.

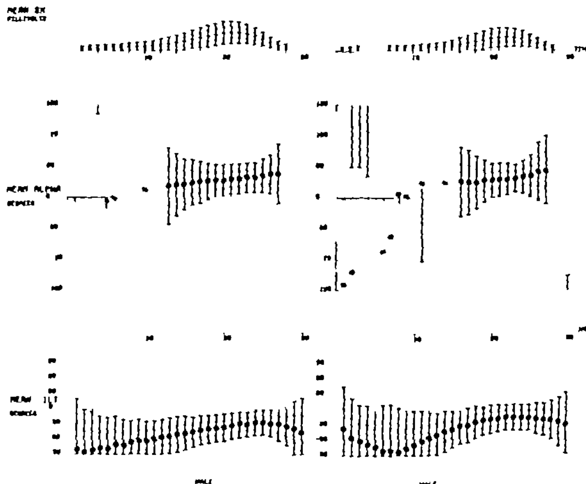


Fig. 4C. Time normalized values of the ST-T segment, mean, and two standard deviation lines plotted at 1/30 of total ST-T segment length, age 40. Frank lead system.

The direction of initial and terminal positions of the QRS complex in terms of α and tilt has served to be a valuable guide for the determination of the site of myocardial infarction, bundle branch block, right and left ventricular hypertrophy, and so on.[9,13] The templates of normals presented here can therefore serve as a range value for these measurements.

The present study of 455 individuals is in good agreement with a previous study of 150 individuals which was limited to the QRS complex.[1] The same wide scatter of QRS during the central portion is seen here. A solid model which was constructed in our laboratory on the basis of a limited number of individuals of one group gave the impression that the cluster of vector heads representing a number of individuals at a given instant of time has an ellipsoid shaped appearance. This ellipsoid seems to travel with its major axis somewhat tangential to the mean spatial loop. Between 30 and 40 msec. the ellipsoid turns backward and presents its smallest projection in the frontal plane which to some extent explains the narrow scatter. In reviewing the scatter range of α it becomes clear why ECG interpretation always has insisted that Q values in limb leads exceed 30 to 35

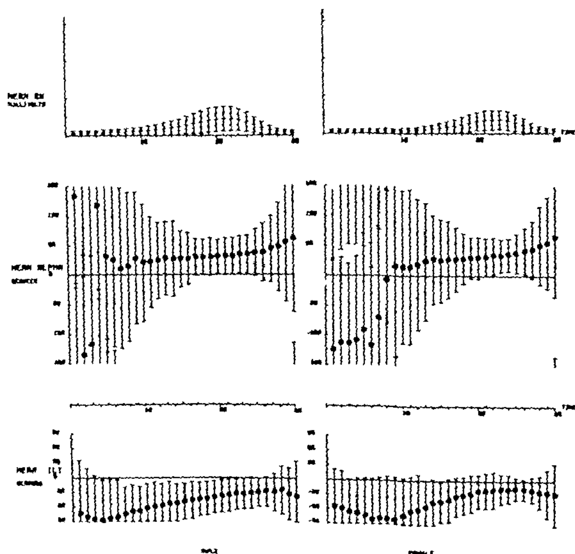


Fig. 4D. Time-normalized ... of the ST-T segment mean, and two standard deviation values plotted ... 1/30 of total segment length, age 50. Frank lead system.

msec. before being classified as abnormal because it is exactly at this time that the scatter of normal individuals disappears and that the template becomes meaningful. For tilt this is different. At 5 msec. some backward tilt is seen in the template but this could be a noise factor at a time when spatial magnitude values are very small. Between 10 and 25 msec., no backward tilt values are seen in any age or sex group. This is in agreement where Q waves of less than 40 msec. duration in V and V are significant.

That the spatial magnitude values at 30 msec. of QRS are relatively larger in the female than in the male groups (Figs. 3A and 3B) when compared to the peak value and that the opposite holds true at 60 msec. may be attributed to a relative right ventricular preponderance in the female subject and left ventricular preponderance in the male. In support of this hypothesis we found (1) statistical radiologic measurements revealed characteristic differences between the male and female heart which were described by the authors as "aortic configurations" of the male and "pulmonic configurations" of the female heart. (2) the mean systolic blood pressure of male individuals in the

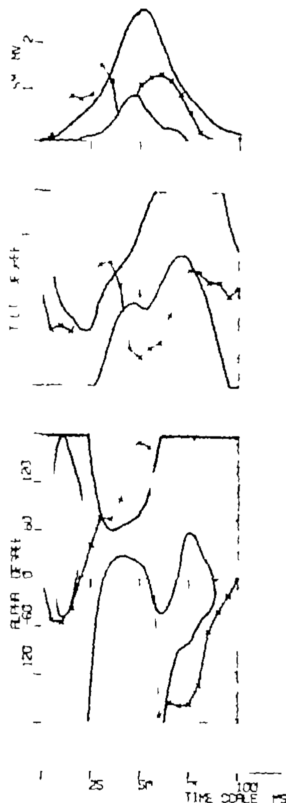


Fig. 7 Spherical coordinates of QRS complex of 16-year-old boy plotted by an incremental plotter which serves as a output device t small digital computer (PDP-8). The record represents typical right ventricular overwork pattern of an trial septal defect

computer.[24] These ranges are now used in a small digital computer as template values (Fig. 7).

Summary

A study of 455 normal individuals divided into four decades and both sexes i presented The lead system employed is that of Frank. The data are presented as mean and two standard deviation values of the spherical coordinates de scribing the instantaneous heart vector of P QRS, and T Einthoven angle α and its angle tilt with the frontal plane were selected to describe the heart direction This set of spheric il angles is just as simple to conceive as azimuth and elevation but h i the advantage of correlating with the traditional heart axis orientation The method may be described as presenting the st itistical range of the instantaneous spatial heart axis as a function of time The areas of narrow scatter in this d splay correlate well with electrocardiographic experience Characteristic differences be tween male and female subjects, particu larly in the T wave pattern are described. The limitation of this method are two-fold (1) this study is based on the assumption that the cardiac generator can be represented by a single equivalent d pole and (2) the statistical decision regions employed here are only a first approxima tion The advantage however i that once stati tical envelopes as presented in this report are available this method can be performed by analogue or small digital computer techniques.

REFERENCES

1 Fra k F A accur t clinicall practical system for spatial ectorc rdiography Circulation 13 737 1956.
2 von der Groeben J The spatial frequency distribution of the QRS loop as studied on 154 normal ind iduals, Am Heart J 59:675 1960.
3. Toole J G on der Groeben, J nd Sprack, A The periodic abnormalities of the temporo-spatial QRS ector in isolated right entricular verwork, Am H rt J 65 77 1963
4 Toole J C on der Groeben, J and Sprack, A. The calculated temporo-spatial heart vector in proved isolated left entricular overwork, Am Heart J 65:537 1963.
5 Geselowitz, D B. Dipole theory in electrocardiography Am. J Cardiol. 14:301 1964
6. Horan, L. G Flowers, N C., and Brody D A

Principle factor waveforms of the thoracic QRS complex, Circulation Res. 15:131, 1964.
7. Horan, L. G., Flowers, N. C., and Brody, D. A.: The limits of information in the vectorcardiogram, Am. Heart J. 68:362, 1964.
8. von der Groeben, J.: Decision rules in electrocardiography and vectorcardiography, Circulation 36:136, 1967.
9. Taccardi, B.: Distribution of heart potentials on the thoracic surface of normal human subjects, Circulation Res. 12:341, 1963.
10. Abildskov, J., Ingerson, W., and Hisey, B.: A linear time scale for spatial vectorcardiographic data, *Circulation 11:556, 1956.*
11. Grant, R.: Clinical electrocardiography, New York, 1957, McGraw-Hill Book Company, Inc.
12. Hurst, J. W., and Woodson, G. W.: Atlas of spatial vector electrocardiography, New York, 1957, Blakiston Company.
13. Schaefer, H.: Das Elektrokardiogramm: Theorie und Klinik, Berlin, 1951, Springer-Verlag.
14. Schmidt, J., and Rampmeller, P. D.: Die Herzformen des Mannes und der Frau im Roentgenbild, Arch. f. Kreislaufforschung 25:163, 1957.
15. Gordon, T.: Blood pressure of adults by age and sex, United States Department of Health, Education and Welfare, Washington, D. C., 1964, 1960-1962.
16. Pipberger, H. V., Goldman, M. J., Littmann, D., Murphy, G. P., Cosma, J., and Snyder, J. R.: Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men, Circulation 35:536, 1967.
17. Duchosal, P. W., and Moret, P.: Individualité de l'électrocardiogramme étudiée par la vectorgraphie, Cardiologia 32:129, 1958.
18. *Dower, G. E., et al.: The polar cardiograph: terminology* and normal findings, Am. Heart J. 69:355, 1965.
19. Dower, G. E.: The polar cardiograph: diagnosis of myocardial infarction, Am. Heart J. 69:369, 1965.
20. Fisher, D. D., von der Groeben, J., and Toole, J. G.: Vectorcardiographic analysis by digital computer: selected results, Technical Report CS21, Palo Alto, Ma. 7, 1965, Computer Science Department, Stanford University.

Amplitude probability densities of electrocardiograms

James A. Cronvich, M.S.*
David J. Ahlgren, M.S.**
George E. Burch, M.D.***
New Orleans, La.

A complex periodic wave form can be characterized in many ways. The frequency spectrum from Fourier analysis has been used most frequently, but the amplitude probability distribution characteristic or the amplitude probability density characteristic (APD) from probability analysis frequently has advantages. If a wave form has an instantaneous amplitude v and during the time interval T has maximum and minimum amplitudes V_{max} and V_{min}, its probability distribution characteristic for the interval T is a plot with v as the independent variable of the fraction of T during which the amplitude is below v. Thus the probability distribution $P = 0$ for $v \leq V_{min}$ and $P = 1$ for $v \geq V_{max}$. The amplitude probability density (p) at any v is equal to dP/dv, the slope of the probability distribution characteristic for that v. If a periodic wave form with period T is sampled over the period with equal increments of amplitude Δv, its amplitude probability density for any voltage v is proportional to the fraction of T during which the amplitude is between v and v + Δv.

In electrocardiography the amplitude, the duration, and the notching and slurring of the various complexes are used for interpreting the electrocardiogram (ECG). It was expected, therefore, that the APD of the ECG would present, perhaps more emphatically than the ECG itself, this information for electrocardiographic interpretation. Although the APD can be determined by point-by-point sampling of the wave form and digital computer calculations, it was decided to use an analogue technique. Blackman and Middleton[1] have shown that if a periodic wave of frequency w(t) is frequency modulated by another wave of frequency $w_m(t)$ to a large index of modulation $\Delta w/w_m$, the voltage amplitude of the envelope of the frequency spectrum of the resultant wave approximates the square root of the APD of the modulating wave. Therefore, equipment to apply this FM method was assembled.

Method

A block diagram of the circuit arrangement used in this study is shown in Fig. 1. The periodic wave form whose APD is to be determined frequency modulates a high-frequency oscillator whose output amplitude is held constant. The output of the oscillator is fed into a wave analyzer

Supported by grants from the United States Public Health Service, the Rudolph Matas Memorial Fund for the Kate Prewitt Hess Laboratory, and the Rowell A. Billups Fund for research in heart disease.
Received for publication Aug. 21, 1967.

*Department of Electrical Engineering and Department of Medicine, Tulane University.
**Formerly, Department of Electrical Engineering and Department of Medicine, Tulane University; now with the University of Michigan.
***Department of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans, La.

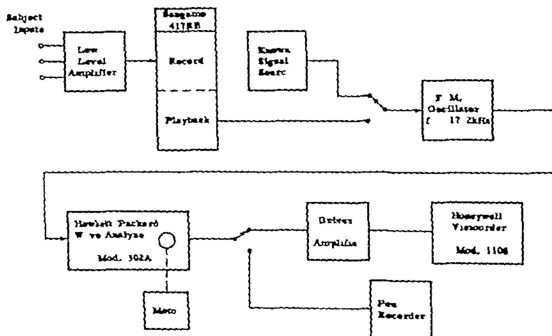


Fig. 1. Block diagram of circuit for recording amplitude probability densities of ECG's.

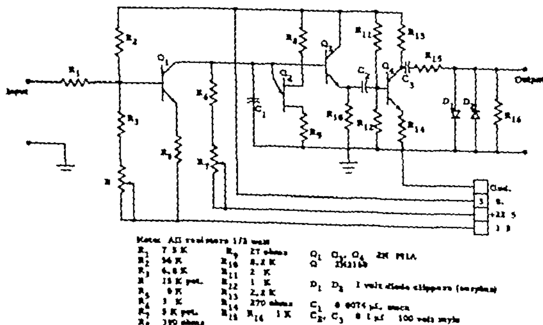


Fig. 2. The FM oscillator and modulator

which se ms d wly over the fund mental spectral range of the oscillator The output of the wave analyzer i recorded on a strip chart recorder

The rcuit f the frequency modul ted (FM) oscillat r hown in F g 2 Q a unijunction tr n t r is used as a saw tooth oscillat r wh se frequency approxi mated 17 t ant Hertz in waves (kHz) i determ ned by th urrent upplied through R_1 to the base f transi tor Q In effect variations in th current ch nge the tim on t nt f th c rcu t involving Q and ap it r C Transistor Q and Q constitute a buffer amplifier between the sawtooth oscillator and the output terminals Diodes D_1 and D_2 clip the out put voltage to limit its amplitude The frequency modulation is essentially linear with input voltage for the range ±1 volt

Performance with waves of known APD characteristics Comparisons of theoretic and experiment l APDs of some familiar w ve form are shown in Figs. 3 through 7 Figs. 3 4 and 5 show the compari sons for sine w ves of 5 2 and 0.25 Hz respectively The theoretic curves are *normalized to the level at zero volts.* Figs

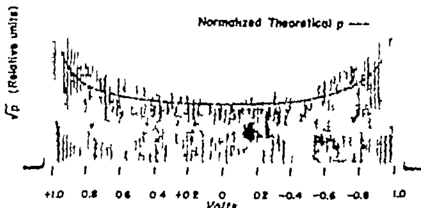


Fig 3 Experimental nd theoretic l APD of 5 H ine w

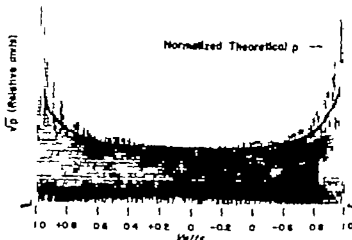


Fig 4 Experimental and theoretical APD of 2 H sine wa e.

6 and 7 show the comparisons for triangular waves of 1 and 0.25 Hz respectively. In Figs. 4 and 5, particularly the latter, the stepped character of the envelope shows the effects of the diode limiters which are used in the function generator (which supplied the "sine wave" input signal) to convert a triangular wave into the sine wave. Visually, the "sine wave" itself was quite smooth.

With an ideal wave analysis, the plots would show individually the center frequency and the many side frequencies of the frequency modulated wave. The wave analyzer, however, has a 7 Hz bandwidth, and therefore, many frequency components, especially with the lower modulating frequencies, lie within this bandwidth window.

Observations of the performance with lower modulating frequencies indicate that the dynamics of the recorder-output system of the wave analyzer are important at modulating frequencies below approxi-

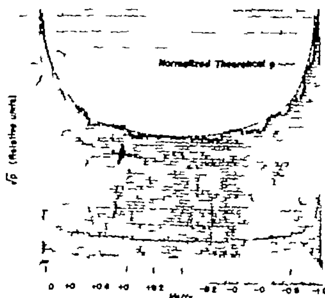


Fig. 5. Experimental and theoretical APD of 0.25 Hz sine w

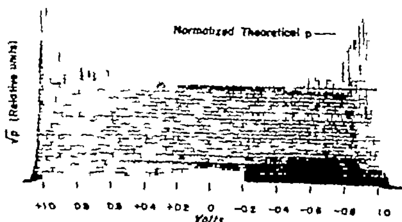
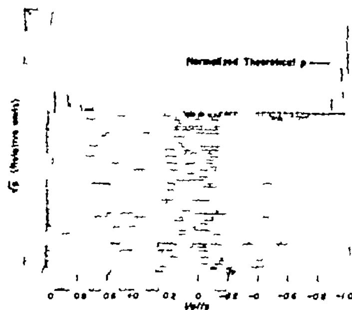


Fig. 6. Experimental and theoretical APD of 1 Hz triangular av



I g 7 I perma t I nd heoret   I A I D f 0 25 H triangular wave

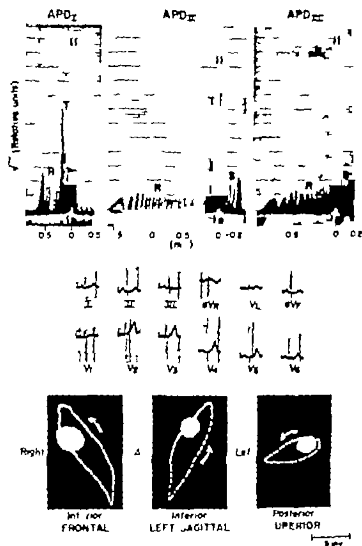


Fig 8 APD of ECG and VCG of a normal huma bei g

mately 1 Hz. With such low modulating frequencies, the recorder-output signal is a series of pulses delivered whenever the changing frequency from the FM oscillator is within the passband of the slowly scanning wave analyzer. These pulses decay as the oscillator signal sweeps beyond the passband and are practically zero when the signal returns through the passband. Ideally the amplitude of these pulses would be proportional to the time that the oscillator signal was within the passband of the wave analyzer and the plot would consist of a series of pulses whose amplitudes were proportional to p instead of $\sqrt{p}$. These effects are shown in Figs. 3, 4, and 5. In these cases, system parameters were unchanged and only the *frequency of the modulating sine wave was* changed. The plots for the 5 and 2 Hz waves are essentially alike; however, the amplitude at the center of the plot for the 0.25 Hz wave is over 2.5 times those of the 5 and 2 Hz waves. A similar effect is shown with the triangular waves in Figs. 6 and 7.

APD characteristics of ECG's. As demonstrated with waves of known characteristics, the method employed in this study has only limited accuracy; however, the results obtained with ECG's are interesting. Since it was decided to use a 20-minute scan of the wave analyzer over the FM spectrum in order to obtain sufficient detail, the ECG's were FM recorded on magnetic tape. Tape sections containing 1 cycle of ECG were carefully spliced into tape loops at the isoelectric T-P interval. The demodulated output of

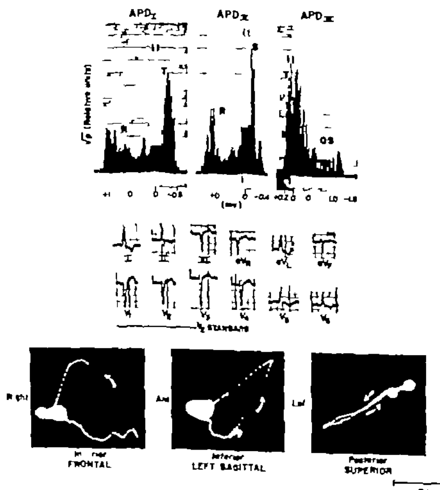


Fig. 9. APD of ECG and VCG of human being (abnormal 1) (left ventricular hypertrophy).

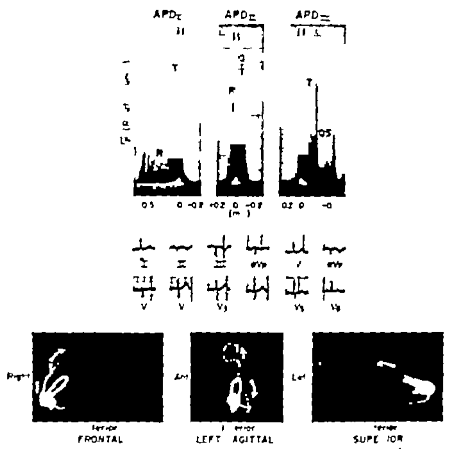


Fig. 10. APD of ECG and VCG of human being (abnormal) ... posterior myocardial infarction.

the tape recorder was used as the input signal to the FM oscillator of the probability density analyzer circuit. It would have been possible, of course, to FM record the ECG onto the magnetic tape and to use the direct mode playback to supply the FM signal for the wave analyzer. This method was not used because it was considered desirable to be able to use different tape speeds for experimental purposes.

The wave analyzer was motor driven to scan slowly over the major spectral range of the FM oscillator as the tape loop continuously repeated the 1 cycle of the ECG.

Discussion

The method reported herein has, despite its limitations, produced some interesting results. Slurring and notching, which are often difficult to see in the conventionally recorded ECG, are usually quite evident in the APD's, as indicated in Figs. 8 to 10.

A study of over 00 ECG's shows that, as expected, the APD's of the normal ECG's are different from those of the abnormal ECG's and that the various kinds of abnormal ECG's differ from one another. The clinical value of the APD of the ECG is uncertain at present, but further investigation is necessary to determine this point.

Three examples of the more than 200 APD recordings of ECG's obtained so far are shown in Figs. 8 to 10. The respective ECG's and spatial vectorcardiograms are included for comparison. APD_I, APD_{II}, and APD_{III} were obtained for a single cardiac cycle of the respective standard limb leads of the ECG as described above. The notch labeled *m* located on the baseline of each APD recording marks the isopotential region of the ECG.

As shown in the figures, components to the left are the results of positive deflections of the ECG and components to the

right are the results of negative deflections. Usually, but not always, the greatest amplitude of the APD occurs at the isopotential level of the ECG. The outermost left edge of the APD corresponds to the peak of the R wave or the most positive amplitude of the respective lead, whereas the outermost right edge corresponds to the maximal negative deflection of the respective ECG lead. The R, S, T, and other deflections of the ECG can be identified in the APD (Fig. 8). It is probable that the darker deflections oriented among the other respective positive and negative components of the APD are manifestations of superimpositions of complexes. Two cardiac abnormalities (Figs. 9 and 10) are shown for comparison with the normal (Fig. 8).

Theoretic limitations of this FM method have been discussed recently by de Buda. The limitation imposed by the wide band width of the wave analyzer relative to the lower frequency components of the ECG is probably not very serious because the important frequency components of the P, QRS, and T complexes are usually above 2 Hz. Of course, it would be possible to increase all frequency components of the ECG by recording on tape at low speed and playing back at considerably higher speed. The clustering of frequency components as predicted by the Bessel function expansion of FM waves is evident with the 5 Hz sine wave and the ECG, especially that of the normal. A very unsatisfactory characteristic of this method is the amount of time required to plot the APD. Other analogue methods have been considered, for example Clarke's, but probably a rapid sampling analogue-to-digital converter combined with digital computer analysis will permit beat-to-beat analysis of the ECG.

Summary

An FM method for determining approximately the APD of periodic wave forms has been studied and applied to ECG's. The results obtained with ECG's indicate that the APD makes notching and slurring more evident than does the ECG and that it may have some advantages over the ECG in clinical diagnosis, especially in the analysis of the high frequency components of the ECG.

REFERENCES

1. Blackman, N. M.: Limiting frequency-modulation spectra, Information and Control 1:26, 1957.
2. Middleton, D.: An introduction to statistical communication theory, New York, 1960, McGraw-Hill Book Company, Inc.
3. de Buda, R.: Stationary phase approximations of FM spectra, IEEE Trans. on Information Theory IT-12, No. 3:305, 1966.
4. Clarke, K. K.: An electronic probability density machine, IEEE Trans. on Instrumentation & Measurement IM-15, Nos. 1/2:25, 1966.

The significance of foreleg positions in the interpretation of electrocardiograms and vectorcardiograms from research animals

John D. Hill, D.V.M., M.S.
Philadelphia, Pa.

While much electrocardiographic information has been gained through the use of experimental dogs, many reports have commented on the marked variability in the electrocardiograms (ECG's) of different dogs and in serial tracings from the same dog. Although the importance of controlling the foreleg positions has been mentioned in several publications,[7] reports continue to comment on the difficulties of electrocardiography in dogs.[13]

Cagan and Barta[7] reported that the position of the forelegs affected the QRST complexes and that the ECG remained stable when the position of the forelegs was controlled. Cagan indicated that a change in the position of the forelegs had a marked effect in all the common body positions used in electrocardiography of the dog. He stated that a change in the basic body position did not substantially affect the ECG if the position of the forelegs was kept unchanged. Illustrations were presented in both papers, but a statistical analysis was not done.

It is the purpose of this report to re-emphasize that changes in the position of the forelegs of dogs can affect the ECG, to determine statistically the extent of that effect on the mean manifest electric axis of the frontal plane, to determine the stability of serial tracings with controlled body and limb positions, and to determine any effect of foreleg positions on the vectorcardiogram (VCG). While this report will present the results found in dogs, variations in the ECG resulting from changes in the positions of the forelegs have also been observed in cats, guinea pigs, rats, rabbits, goats, sheep, calves, horses, and in the arm positions of one primate (*Macaca nemestrina*).

Material and methods

Electrocardiographic studies. A total of 15 normal dogs were studied. The dogs were untrained, unanesthetized, and included various purebreds and mongrels. In preliminary trials, no marked changes occurred in the ECG with changes in the position of the hindlegs; nevertheless, the positions of the hindlegs were controlled in the present study. For the basic position the dogs were placed in the right lateral recumbent position with the hindlegs

From the Comparative Cardiovascular Studies Unit, Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pa.

Supported in part by grants from the National Heart Institute (HE-4885-07) and American Heart Association (61-G-81).

Received for publication May 17, 1967.

*Post-Doctoral Fellow of the National Heart Institute, United States Public Health Service (1-F2-HE-32,830-01). Address: University of Pennsylvania, School of Veterinary Medicine, 3800 Spruce St., Philadelphia, Pa. 19104.

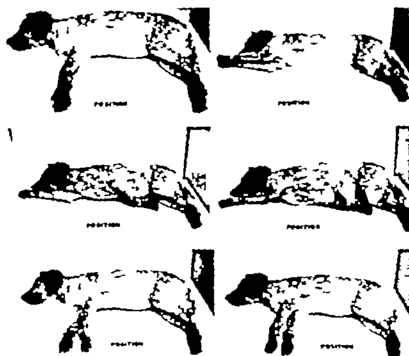


Fig. 1. The six foreleg positions used. The dog was anesthetized for the illustration.

parallel to each other and perpendicular to the animal's longitudinal axis, as in the standing position. On the basis of preliminary trials, six foreleg positions were used as illustrated in Fig. 1. Positions 7 and 8 represent unnatural placements of the left scapula and limb. In the latter positions, the dog was placed in the right lateral recumbent position with the forelegs and hindlegs parallel to each other and perpendicular to the long axis of the body. The forelimbs were firmly held in extension. The vestigial clavicle in the dog permits the scapula to be moved cranially and caudally about 1 to 2 cm. The scapula was moved caudally in position 7 and cranially in position 8.

A total of 12 serial tracings were recorded over a 16-day period in an additional three normal dogs. The ECG's were made at the same time each day with the dogs in the basic position and the forelegs in position 1. The limbs were shaved at the site of the electrodes so that the electrode positions could be repeated accurately.

Standard bipolar and augmented unipolar limb lead ECG's were recorded on a Cambridge Versa Scribe at a paper speed of 25 mm. per second and at a sensitivity of 1 mv. equal to 1 cm. deflection. In some dogs, simultaneous tracings also were recorded on an oscilloscopic recorder (Electronics for Medicine) at a paper speed of 100 mm. per second and twice normal sensitivity. The mean manifest electric axis of the frontal plane was determined by the algebraic sum of the QRS amplitude in Leads I and III. This measurement was chosen because it summarized the changes and simplified the statistical analyses. The QRS complexes selected for measurement were chosen from areas of the tracing in which the preceding and following T-P intervals were exactly on the same level. In those cases where the tracing was not level, a number of complexes were measured and averaged. The complexes were not selected for any period of respiration. All the measurements were made under a magnifying lens (Mag hook-on loupe No. 7). The amplitude for upward deflections was measured from the upper contour of the base line and from the lower contour of the base line for downward deflections. All amplitude measurements less than 0.1 mv. were marked 0.05 mv.

Standard methods of statistical analyses were followed. The significance of differences between paired observations was determined by the paired variate t test. The relationship between the passage of time and the QRS mean manifest electric axis was examined by means of least squares regression analysis.

Vectorcardiographic studies. The effects of different foreleg positions on the VCG were studied in six normal dogs anesthetized with sodium pentobarbital (30 mg. per kilogram intravenously). The dogs were placed in the basic right lateral position, and foreleg positions 1, 3, and 4 were used successively. The frontal, transverse, and left sagittal plane VCG's were recorded for each of the three foreleg positions using both the Wilson and associates equilateral tetrahedron and McFee and Parungao[4] systems. For the horizontal axis in the Wilson system, the exploring electrode (V10) was placed over the dorsal spine of the seventh thoracic vertebra. The dog is viewed ventrally in the frontal plane and cranial to caudal in the transverse plane. In the sagittal plane the dog is viewed from the left side in the normal standing position. This method of viewing the three planes follows standardized electrocardiographic conventions[1] and also follows Helm's[25] suggestions for maintaining trigonometric functions and keeping the zero point constant in all three planes. The VCG's were recorded on an eight channel switched beam oscilloscope (Electronics for Medicine). The VCG's were examined for general configuration of the loops, direction of inscription, maximum QRS vector, and length width ratio.

Results

Electrocardiographic studies. Changes in the position of the forelegs in dogs affected the QRS complex most dramatically, while the P and T waves were affected to a lesser degree (Fig. 2). Table I lists the results of different foreleg positions on the mean manifest electric axis of the QRS complex in the frontal plane. The differences between the means were statistically significant at the 5 per cent probability level or less.

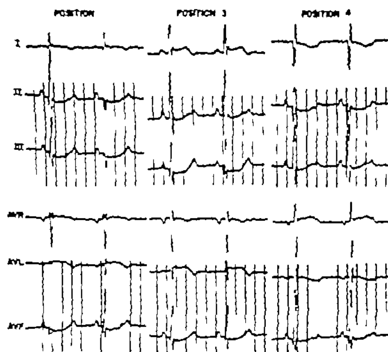


Fig. 2. Simultaneously recorded bipolar limb leads and simultaneously recorded augmented unipolar limb leads illustrating the effect of different foreleg positions. Position 1 was used as the standard position and positions 3 and 4 were the foreleg positions showing the most marked effects. Time lines are at 0.1 second and the standardization was 2 cm. per millivolt.

Table 1 The effect of different foreleg positions on the mean manifest electric axis of the QRS complex in degrees for the frontal plane in dogs and significance of axis deviations from axis determined by position 1

Dog No.	Position							
	1	2	3	4	5	6	7	8
NF1	82	88	55	115	77	85		
NF2	101	96	53	141	89	113		
NF3	90	90	71	150	86	100		
NF4	83	90	65	111	80	92		
NF5	68	85	35	108	66	78		
NF6	67	82	42	141	71	86		
NF7	73	87	42	130	84	90	70	86
NF8	56	80	6	148	24	68	59	82
NF9	73	84	79	95	69	82	72	86
NF10	73	85	30	124	65	68		
NF11	73	84	26	130	62	86		
NF12	71	86	60	116	83	90		
NF13	76	82	28	100	69	74		
NF14	63	83	39	90	50	63	72	72
NF15	78	88	27	101	58	74	68	81
M an	73 1	86 0	44 0	123 6	68 8	83 3	68 2	81 4
		+5 737	−7 256	+8 488	−2 185	+3 932	−0 127	+3 413
p		<0 001	<0 001	<0 001	<0 05	<0 01	>0 90	<0 05

Positions 2 degrees of freedom 1
ositions 7 and 8 degrees of freedom

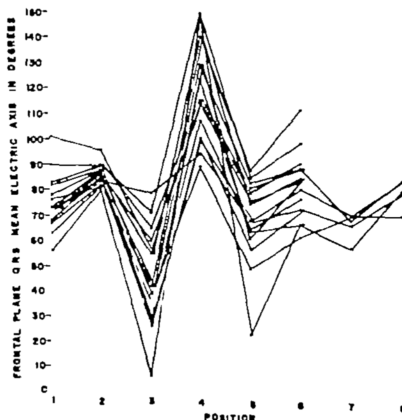


Fig 3 A gr phic representation of the effect of different foreleg positions on the frontal plane QRS mean lectric axis in 15 dogs. The most table position for all he dogs as position 2 ith total range of onl 16 degrees. Positions 7 and 8 represent unnatural placement of the left scapula.

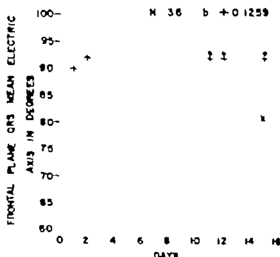


Fig. 4. The daily frontal plane QRS mean manifest electric axes of three dogs plotted with their least squares regression line. The regression coefficient was not significant for the relationship between these mean electric axes and the passage of time. The dots represent a 4-year-old female German Shepherd, X represent a 4-year-old male Beagle, and + represent a 5-year-old male mongrel.

for all five limb positions when compared with limb position 1 as the standard. The most marked changes occurred in position 4. In one dog (No. 8) the frontal plane axis was changed from 56 degrees in position 1 to 148 degrees in position 4, a change of 92 degrees. In position 4 the frontal plane axis in 11 of the 15 dogs exceeded the range of normal dogs (0 to +102 degrees) and would be classed as right axis deviation. The most stable position for all the dogs was position 2 with a total range of only 16 degrees (Fig. 3). When position 8 was compared with position 1, a statistically significant difference at the 5 per cent probability level was achieved although there were a rather limited number of observations.

In three dogs serial tracings were recorded over a 16-day period. The frontal plane QRS mean manifest electric axis plotted for each day and the least squares regression line are shown in Fig. 4. The regression coefficient was not significant for the relationship between these mean electric axes and the passage of time. The ECGs in Fig. 5 are from the dog marked

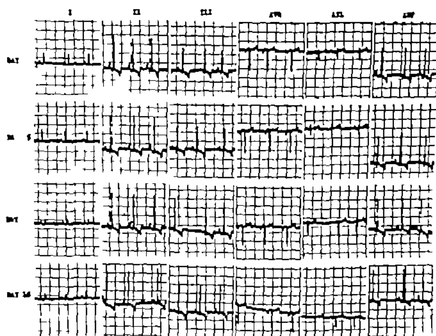


Fig. 5. ECGs from the Beagle (marked by X) in Fig. 4 which had the most marked changes in the frontal plane QRS axis in serial tracings. It can be seen that controlling the limb positions as well as the body position resulted in fairly consistent tracings over many days except for small amplitude changes in lead I. The paper speed was 25 mm. per second and the standardization was 1 cm. per millivolt.

by V s in Fig 4 The ECG s were selected from the days exhibiting the greatest changes. It can be seen that the changes were small and that controlling the limb positions as well as the body position resulted in fairly consistent tracings over an extended period of time The serial tracings were recorded by students using reasonable care and without the aid of any special techniques or devices to control the body and limb positions.

Vectorcardiographic studies The Wilson system scalar leads and VCG s in Fig 6 were obtained from one of the five dogs studied. The configurations of the loops for positions 3 and 4 were markedly altered from that found for position 1 in the frontal and transverse planes, but little change occurred in the sagittal plane. The direction of inscription was altered most in the frontal plane (Table II) In general the maximum QRS vector was altered more in position 3 than in position 4 in all three planes. The direction of change however was not consistent. The length-width ratios were considerably decreased in the frontal and increased in the transverse planes but there were only small differences in the sagittal plane. The McFee system scalar leads and VCG s obtained with different foreleg positions are illustrated in Fig 7 There was little effect on the configurations

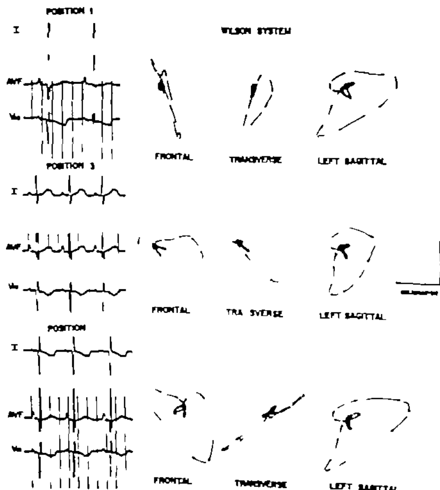


Fig 6 Scalar leads and VCG recorded by Wilson equilateral etrahedron system illustrating the effect of different foreleg positions Time lines in the scalar leads are 0 1 second. The VCG has been retouched. The dashes narrow in the direction in which the loop is inscribed.

Table III. The effect of different foreleg positions on the Wilson system VCG's in dogs

Lead	Direction of inscription position 1, 3 and 4			Maximum QRS vector in degrees position 1, 3 and 4			Length-width ratio in positions 1, 3 and 4		
	1	3	4	1	3	4	1	3	4
Frontal plane									
VI 1		w	ccw	55	20	45	2 6	3 6	2 2
VI 2	w			72	10	80	8 4	1 4	1 7
VI 3				85	125	65	8 8	1 4	1 9
VT 4				70	13	65	9 2	1 4	2 1
VI 5	w	w	w	87	95	73	15 9	1 9	3 1
Transverse plane									
VF 1	w	w	w	−67	25	−45	1 8	4 0	7 2
VI 2	w		w	94	35	150	2 4	3 8	15 7
VI 3	w w		w/	−90	32	145	5 0	9 4	11 9
VI 4	w			105	35	140	2 8	3 9	33 0
VI 5	w	w	w/	100	45	145	6 6	7 1	14 7
Sagittal plane									
VI 1	w	w/ w cw		−56	55	−50	1 5	3 0	2 2
VI 2		w		10	80	0	1 6	1 1	1 9
VI 3	cw	cw	ccw	−35	−43	−20	2 1	1 6	2 1
VI 4	w	w		120	105	115	2 1	1 4	2 2
VF 5	w	w	w	−15	−15	−16	2 6	2	2 9

w clockwise ccw counterclockwise

of the loops in contrast to the Wilson system. The results for the direction of inscription, maximum QRS vector, and length width ratio are given in Table III. In general there were only minor changes in these measurements as a result of different foreleg positions.

Discussion

The present study demonstrated that even minor changes in foreleg position resulted in statistically significant differences in the ECG when compared to a control position. Andre[11] and Lannek[12] stated that the QRS mean electric axis of the dog was so wide that it was not clinically useful. In the present study, the total range in control position 1 was 45 degrees. In the same 15 dogs this range was reduced to 16 degrees in position 2. In 70 normal dogs, the QRS frontal plane mean electric axes ranged from 0 degrees clockwise to +102 degrees in position 1 (unpublished observations). Using position 1 in a group of 68 dogs with right ventricular hypertrophy from congenital and spontaneously acquired heart lesions, 79.4 per cent had frontal plane QRS mean electric axes outside the range of the normal dogs. This finding indicates that the QRS mean electric axis of the dog is a useful diagnostic characteristic and might be further enhanced by the use of position 2; however, there may be difficulties in restraining an uncooperative awake dog in this position.

Many authors[4,12,13] have noted the wide variability in the ECG's of different dogs and in serial tracings from the same dog. Lombard and Witham have reported on the importance of body position in electrocardiographic recordings. Some authors[4,12] concluded that the supine position is superior to the lateral position and resulted in improved reproducibility in serial tracings. In their experiments, the dogs were placed in V shaped wooden troughs with the legs tied to the sides of the trough. Such methods would not only maintain uniform body position but also would improve the uniformity of limb position. Gonin[13] found that the spontaneous changes in mean electric axis in serial tracings were

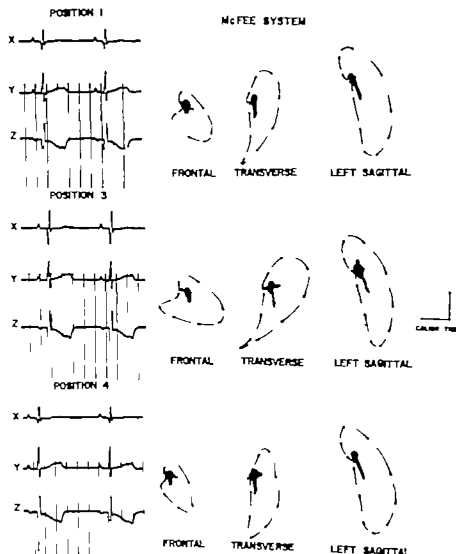


Fig. 7. Scalar leads and VCG recorded by the McFee system illustrating the effect of different foreleg positions. From the same dog as in Fig. 6. Time lines in the scalar leads are at 0.1 second. The VCG has been retouched. The dashes narrow in the direction in which the loop is inscribed.

smaller in the sternal position than in the right lateral recumbent position. It was stated that the dogs were allowed to place their legs in whatever position was comfortable. The lateral position in the dog certainly permits greater freedom of movement than the sternal position.

The standing and sitting positions in the dog usually give unsatisfactory tracings as a result of muscle tremors. The supine position is not well tolerated in the awake untrained dog. The prone position can be used, but it is difficult to restrain the dog in this position if the dog is not cooperative. The right lateral position is usually well tolerated and has the advantage that the limb positions can be controlled by an assistant. The assistant faces the spine of the dog and with the left hand and forearm controls the hindlegs and caudal end of the dog while the right hand and forearm control the forelegs and neck of the dog. In this manner the body and limb positions can be well controlled, the dog can be

Table III The effect of different foreleg positions on the McFee system vectorcardiograms in dogs

Dog No.	Direction of inscription in position 1, 3, and 4			Maximum QRS vector in degrees positions 1, 3, and 4			Length-width ratio of positions 1, 3, and 4		
	1	3	4	1	3	4	1	3	4
Frontal plane									
VF1	cw		cw	5	6	6	2 8	3 7	2 6
VF2	cw	cw	cw	38	25	50	2 3	3 1	2 0
VF3	cw ccw	cw	cw	98	105	120	3 2	1 7	1 5
VF4	cw	cw	cw	57	40	57	1 7	1 5	2 0
VF5	cw	cw	ccw/cw cw	55	47	70	3	4 0	3 1
Transverse plane									
VF1	cw	cw		−54	−17	−52	3 7	2 6	3 6
VF2	ccw	ccw		127	125	123	2 1	2 2	1 6
VF3	cw/ccw	cw/ccw	cw/ccw	85	92	95	5 7	4 1	4 4
VF4	cw	cw	cw	102	116	98	3 0	2 8	3 1
VF5	cw	ccw	ccw	66	55	90	4 2	2 7	4 7
Sagittal plane									
VF1	cw	ccw	ccw	−94	−94	−9	6 8	7 7	7 3
VF2	ccw	ccw	cw	70	72	69	1 9	2	2 1
VF3	ccw	ccw	ccw	−70	−70	−73	2 6	2 8	2 6
VF4	cw	ccw	ccw	75	75	75	2 9	3 3	2 7
VF5	cw	ccw	ccw	70	60	60	1 8	1 9	1 9

*cw, clockwise; ccw, counterclockwise.

forcibly restrained if necessary and tracings can be recorded quickly with excellent reproducibility

Altering the position of the forelegs resulted in a change in the direction of inscription in the VCG s of some dogs. In 12 instances altering the position of the forelegs not only changed the direction of the inscription but also altered the configuration of the loops. Horan and co-workers[22] found slight alterations in the direction of the inscription in the frontal plane when the body of the dog was rotated or tilted about its transverse or longitudinal axes. In general the different foreleg positions had a greater effect on the VCG s of the Wilson system than on those of the McFee system The greatest changes were observed in the frontal plane of the Wilson system and the smallest changes occurred in the sagittal plane of the McFee system for all items examined The P and T loops appeared to be altered about the same as the QRS loops, but were too small to permit detailed analysis. While these findings indicated that the McFee system produced more consistent results and therefore appeared to be a more reliable vectorcardiographic system in the dog the greatest consistency was obtained with standardized foreleg positions in both systems.

That the position of the heart is important was indicated by Waller[24] in 1888 when he described the electrocardiographic findings in dextrocardia with situs inversus in humans. Einthoven[25] pointed out that rotation and position of the heart can alter the ECG in man He illustrated this by the usual tracings seen in dextrocardia with situs inversus and then he reversed the right and left arm leads to show that it resulted in a normal tracing Simonson[26] has discussed in detail the effect of technical physiological and constitutional variables on the ECG of man Many of these variables also affect the dog s ECG In addition to the effect of foreleg positions on the ECG of dogs, Detweiler and Detweiler and Patterson have noted that the QRS electrical axis also varies with the body conformation Gonin[11] reported that narrow-chested dogs such as the Collie French Poodle and German Shepherd have a more constant and vertical heart axis, while

broad-chested dogs such as the Cocker Spaniel and Boxer breeds have a more horizontal and variable heart axis. The Dachshund with a broad thorax and vertical electrical axis, is an exception.

From present and past work, it is apparent that many known and unknown factors contribute to the variations seen in ECG's. Therefore it may be concluded that effort expended to control possible variables will lead to greater uniformity in ECG's of different animals and in serial tracings from the same animal

Summary

The effects of various foreleg positions on the ECG and VCG have been studied in dogs. A statistically significant effect on the frontal plane QRS mean manifest electric axis was found for all the foreleg positions studied when compared to the control position. Several changes due to foreleg positions were noted in some planes of the Wilson equilateral tetrahedron and McFee system VCG's. Consistent serial ECG's were obtained over a 16 day period when the body and limb positions were carefully controlled

The author thanks Dr D A. Abt for assistance in the statistical analyses and M R. Iannuzzi for technical assistance. The author is indebted to Drs. D K. Detweiler and E. N Moore and other members of the Comparative Cardiovascular Studies Unit for their helpful advice and criticism

REFERENCES

1 Katz, L N Soskin, S., and Frisch R. Variations in contour of the records found in serial electrocardiograms of the dog Proc. Soc Exper Biol. & Med. 32:208, 1934.
2 Harris, B R and Hussey R. The electrocardiographic changes following coronary artery ligation in dogs, Am Heart J 12 724, 1936
3 Lalich J Cohen, L., and Walker G The frequency of electrocardiographic variations in normal unanesthetized dogs. Am Heart J 22 105 1941
4 Peterson, R S Ricketts, H T Brewer N R. Lints, H. A Test C E and Topakova, N A Electrocardiogram of the Beagle dog Proc Soc Exper Biol & Med 77:330, 1951
5 Horwitz, S. A Spanier M R., and Wiggers, W C The electrocardiogram of the normal dog. Proc Soc Exper Biol. & Med. 84 121, 1953
6 Lombard E. A and Witham, C Electrocardiogram of the anesthetized dog. Am. J Physiol 181:567 1955
7 Cagan, S and Barta, E Die Bedingungen des Konstanten Elektrokardiogramme beim Hunde, Ztschr f Kreislaufforsch. 48:1101 1959
8. Cagan, S. Prispevok K Elektrokardiogramu U Psa, Bratislavsk, Lek Listi. 39:540, 1959
9 Detweiler D K Cardiovascular disease in animals Clinical considerations, in Luisada, A. A editor Cardiology New York, 1961 McGraw Hill Book Company Inc., Vol. 5 Sec. 27 p. 10.
10. Detweiler D K. Advances in canine cardiology Small Animal Clinician 2:315 1962
11 Detweiler D K., and Patterson, D F The prevalence and types of cardiovascular disease in dogs, Ann New York Acad. Sc. 127:481 1965.
12 Newton, C Ellis A and Zarnoski, S. Standardization of electrocardiographic recordings repeated experiments on supine anesthetized dogs, Proc. Soc Exper Biol. & Med. 104:182, 1960
13. Goum, P Über die Lage der elektrischen Herzachse beim Hund, Inaug Diss Bern., 1962
14 Burman, S. O Panagopoulos, P and Kahn, S The electrocardiogram of the normal dog. J Thoracic & Cardiovas. Surg 51:379 1966
15. Crawley G J and Swenson, M J The canine electrocardiogram prior to and following production of cardiac lesions, Vet. Med Small Animal Clinician 61:363 1966.
16 Croxton, F F Elementary statistics with applications in medicine and the biological sciences, New York, 1959 Dover Publications, Inc pp. 114 240-242.
17 Wilson, F N Johnston F D and Kossman, C. E. The substitution of tetrahedron for the Einthoven triangle, Am. Heart J 33:594 1947
18 McFee, R and Parungao, A An orthogonal lead system for clinical electrocardiography Am Heart J 62:93, 1961
19 Committee on electrocardiography American Heart Association Recommendations for standardization of electrocardiographic and vectorcardiographic leads Circulation 10:564, 1954.
20 Helm, R A Vectorcardiographic notation, Circulation 13:581 1956
21 Andre, T Enlargement of the heart with congestive heart failure in dogs, Nord. Vet. Med 7:905 1955.
22. Lannek, N A clinical and experimental study of the electrocardiogram in dogs, Med Clin Royal Vet. College, Stockholm, 1949
23. Horan, L Burch, G. E., and Cronvich, J A Spatial vectorcardiograms in normal dogs, Circulation Res 5 133 1957
24 Waller A. D Introductory address on the electromotive properties of the human heart, Brit. M. J 2 751 1888
25. Einthoven, W The different forms of the human electrocardiogram and their signification, Lancet 1:853 1912.
26. Simonson, E. Differentiation between normal and abnormal in electrocardiography St. Louis, 1961 The C. V Mosby Company pp. 59 131

Electrical alternans of components of action potential

Morris Kleinfeld, M.D.
Edward Stein, Ph.D.
Brooklyn, N. Y.

In a previous publication reported in this JOURNAL the authors presented a brief review of recent developments in clinical and experimental electrical alternans. Particular emphasis was given to observations made by means of single cell electrical recording. Experimentally, electrical alternans has been produced in both contractile and conductive fibers in a number of species. The phenomenon was usually transitory, unrelated to the heart rate and more often not associated with decreased cardiac contractility. Alternation of four types was observed: (1) in the rate of depolarization, (2) in the rate of repolarization, (3) in the magnitude of the action potential, and (4) in the magnitude of hyperpolarization. The alternation in the rate of depolarization and of repolarization of the action potential correlated with the electrical alternans of the QRS complex and T wave, respectively.

More recently, the authors have observed the occurrence of electrical alternans in both Purkinje and ventricular fibers of the dog heart following the administration of propranolol in concentrations of 1.5 × 10^{-4}M or greater. Another interesting observation was the occurrence of a separation of the cardiac action potential into a spike (fast) and plateau (slow) component in either fiber. In two instances, there was electrical alternans of both the spike and plateau component. To our knowledge this finding has not been reported previously and hence is the basis of this report.

Material and methods

The procedure for simultaneous recording of intracellular potentials from Purkinje and ventricular fibers of the dog heart has been described in a previous publication. Briefly, the false tendon–papillary muscle preparation was placed in a temperature-controlled perfusion chamber and bathed in a slowly flowing Tyrode solution into which a mixture of 95 per cent O_2 and 5 per cent CO_2 was bubbled continuously. The bath temperature was maintained between 35 and 37° C. Transmembrane action potentials from Purkinje and ventricular fibers were recorded simultaneously using intracellular glass capillary microelectrodes. The preparation was stimulated at the false tendon. Rectangular pulses of 5 msec. duration and usually at a frequency of 60 per minute were supplied by a Grass stimulator and stimulus isolation unit. Propranolol was administered as a constant perfusion in concentrations

From the Department of Medicine, Maimonides Medical Center, and State University of New York, Downstate Medical Center, Brooklyn, N. Y. 11219
Supported by a grant from the United States Public Health Service (HE-09377).
Received for publication June 7, 1967.
*Clinical Associate Professor of Medicine, State University of New York, Downstate Medical Center, and Associate Attending Physician, Maimonides Medical Center, Brooklyn, N. Y. Address: Maimonides Medical Center, 4802 Tenth Ave., Brooklyn, N. Y. 11219.
**Research Associate, Department of Medicine, Maimonides Medical Center, Brooklyn, N. Y.

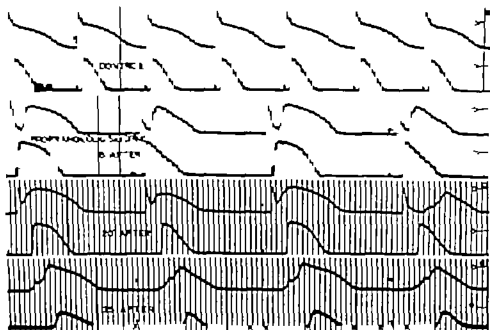


Fig *1* Effect of 1 5 × 10 M propranolol on the Purkinje and entricular fiber action potentials of dog heart. The upper records are from the Purkinje fibers nd the lower records from the entricular fibers. A control *B* 5 minutes after the dministration of 1 5 × 10^{-4}M propranolol, there is lowing of the heart rate The control rat could not be maintained by increasing the pulse stimulus intensity Stimulus frequency had to be decreased in order to dri preparation t constant rat The Purkinje fiber action potential show a prominent spike component and deep notch followed by slow component there is electrical alternation of the slow component there is also electrical alternans of the entricular fiber action potential *C* 20 minutes after the fourth action potential of the Purkinje fiber how distinct separation between the spik and slow wave. There is an increase latency bet een Purkinje and entricular fiber action potential pulse stimulus intensity is increased. *D* 35 minutes after the Purkinje fiber action potential show marked decrease in spike magnitude nd the rat of depolarization of the spik s lowed. There is electrical alternans of both the spike and slow av components of the Purkinje fiber The entricular fiber show decrease in magnitude of the action potential. Abscissae = time Time lines, 0 04 second gain, 1 0 cm. = 50 mv Gain is indicated by ertical bars t left of each potential in top record Dotted lines t right of each action potential indicate zero (0) level of potential

varying from 1 5 × 10^{-4}M to 1 5 × 10^{-4}M The action potentials were mon tored on a dual beam oscilloscope (Tektronic 545A) and recorded on a Sanborn Twinbeam model 6 electrocardiograph

Results

Propranolol (1 5 × 10^{-5} to 1 5 × 10^{-4}M) produced separat on of the cardiac action potential into a fast (spike) and slow (plateau) component n four of 12 experi ments. In three of th four experiments, the separation nto the two components was observed in the Purkinje fiber and in one instance in th entricular fiber It was not observed in both fibers simultaneou ly The appearance of p ke nd plateau separation was associated w th an increase in latency Electrical alternans of both the spike and plateau phases was present in two of the four experiments and both oc curred in the Purkinje fiber (F g 1) In eight of the twel e experiments there was no discernible separation of the cardiac action potential nto a fast and slow com ponent However the electrical alternans was seen n four In two of these nstances, the alternation was present n both fibers simultaneously In addition to the occu rence of electrical alternans, propranolol produced other toxic changes in both fibers, namely a slowing n the rate of depolariza tion a decrease in the size of the overshoot an ncrease in latency and a depression of excitability In Fig 1,*B* the control rate could not be maintained even w th a high

intensity stimulus and to maintain a constant rate the preparation had to be stimulated at a lower frequency.

Discussion

From the studies reported by others[1-4] and from our observations, the characteristic cardiac action potential may under certain influences become altered to either a spike or a spike and slow wave configuration. This separation of the action potential into two components has been observed after the administration of procaine, acetylcholine, and hypertonic solution and also after exposure to low temperature. There is evidence which suggests that the initial fast component (spike) is related to an increase in sodium conductance. There is less solid evidence to explain the occurrence of the slow component (plateau). Faes de Carvalho, Hoffman and Langan demonstrated a sensitivity of the slow component to acetylcholine (ACh) and they suggested that the slow component may be due to a decrease in potassium conductance. Recently, Orkand and Niedergerke[8] indicated that the plateau phase of the action potential of the frog ventricle is related to an increase in calcium conductance although the increase in permeability may not be sufficient to completely account for the potential change.

In regard to the occurrence of electrical alternans in single fibers, the first such report was in the papillary muscle of the dog reported by Hoffman and Suckling in 1954. Subsequently, this phenomenon was observed by the present authors in pacemaker, specialized conductive, and contractile fibers.[1] Alternation in the phases of depolarization and repolarization of the cardiac action potential has been observed. In addition, the present study shows that electrical alternans can involve both the fast and slow components of the cardiac action potential. The available data do not permit the formulation of a single hypothesis to explain the various forms of electrical alternans described. The experimental demonstration of electrical alternans in single cells of intact hearts militates against the general hypothesis that a portion of the myocardium is refractory in alternate beats. Observations in single cells strongly suggest that alternation in rate and extent of transport of ions across the myocardial membrane is involved.

Summary

Separation of the cardiac action potential into a fast (spike) and a slow component (plateau) in both the Purkinje and ventricular fibers of dog heart was observed after the administration of propranolol in concentrations of 1.5×10^{-5}M or greater. In addition, propranolol produced electrical alternation of both components, a finding which has not been reported previously. Other toxic effects were a slowing in rate of depolarization, a decrease in overshoot, an increase in latency, and a depression of excitability in both fibers. Although the appearance of spike-plateau separation was associated with latency shifts the latter does not adequately explain the separation nor the electrical alternans of the two components.

REFERENCES

1. Kleinfeld, M., Stein, E., and Kossmann, C. E.: Electrical alternans with emphasis on recent observations made by means of single-cell electrical recording, Am. Heart J. 65:495, 1963.
2. Kleinfeld, M., Stein, E., and Murphy, B.: Parachloromercuribenzoate on action potentials of Purkinje and ventricular fibers of dog heart, Am. J. Physiol. 206:975, 1964.
3. Matsuda, K., Hoshi, T., Kameyama, S., and Yagi, S.: Effect of procaine on the membrane potential of dog ventricle, J. Physiol. Soc. Japan 18:246, 1956.
4. Wright, L. B., and Ogata, M.: Action potential of amphibian single auricular muscle fiber: a dual response, Am. J. Physiol. 201:1101, 1961.
5. Goto, M., Tamai, T., Abe, Y., and Yanaga, T.: An analysis of the intracellular action potential of the cardiac muscle. Part I. The intercellular functional connection and the characteristic small potential, Kyushu J. M. Sc. 12:177, 1961.
6. Trautwein, W., and Dudel, J.: Action potential and mechanogram of cat papillary muscle as a function of temperature, Arch. ges. Physiol. 260:101, 1954.
7. Faes de Carvalho, A., Hoffman, B. F., and Langan, W. B.: Two components of the cardiac action potential, Nature 11:938, 1966.
8. Orkand, R. K., and Niedergerke, R.: Heart action potentials: Dependence on external calcium and sodium ions, Science 146:1176, 1964.
9. Hoffman, B. F., and Suckling, F. E.: Effect of heart rate on cardiac membrane potentials and unipolar electrogram, Am. J. Physiol. 179:123, 1954.

Prolonged partial extracorporeal perfusion

Armand A. Lefemine, M.D.
*Anna Mae Fosberg, R.N.***
*Dwight E. Harken, M.D.****
Boston, Mass.

The limitations of presently available pump oxygenators in clinical use are recognized although problems associated with their extended use are less well defined. These will vary with the type of bypass, the amount of bypass, the character of the pump and, more significantly, the design of the oxygenator. This report presents some of the hemodynamic and metabolic observations of six hour and ten hour venoarterial bypass in healthy dogs when a pulsatile pump and a disposable bubble oxygenator are used.

Method

Adult mongrel dogs were anesthetized with intravenous pentobarbital and placed on an automatic ventilator. A No. 20-25 F plastic cannula was inserted into a jugular vein and advanced to the right atrium for venous return to the extracorporeal system. A No. 14-16 F plastic cannula was inserted into a femoral artery for arterial pump return. The extracorporeal system consisted of a Travenol† 500 disposable bubble oxygenator, a heat exchanger, and the Army pump.‡ Oxygen flow to the oxygenator was approximately 3 L. per minute. The extracorporeal system was primed with 800 c.c. of Ringer's solution. Fresh heparinized blood was collected from donor dogs just prior to the experiment. Body temperature was controlled in the range of 34 to 37° C. Mean blood pressure was measured by a mercury manometer and an intra-arterial cannula. Flow was measured continuously by a Foxboro electromagnetic flowmeter. Samples of arterial blood were taken hourly for duplicate determinations of pH, pO_2, pCO_2, hematocrit, and plasma hemoglobin.

Flow, blood pressure, and hematocrits were used as guides for transfusion. Flows were maintained above 700 c.c. per minute by the addition of heparinized blood or Ringer's solution—selected to maintain the hematocrit between 30 and 40 per cent. Mean arterial pressure below 90 mm. Hg was also used as an indication for additional volume. Heparin (100 mg. per kilogram) was administered just before bypass and supplemented by 50 mg. every four hours. Penicillin and streptomycin were given intramuscularly at the start

This work was supported in part by the United States Public Health Service Training Grant No. 5 T1 HE 5323-07 and Research Grant HL 07090-0.
Received for publication June 1967.
*Formerly Instructor in Surgery, Harvard Medical School, Associate in Surgery, Peter Bent Brigham Hospital, Boston, Mass. Address: 85 Jefferson Street, Hartford, Conn.
**Research Associate, Surgical Research Laboratories, Harvard Medical School.
***Clinical Professor of Surgery, Harvard Medical School; Surgeon, Peter Bent Brigham Hospital, Boston, Mass.
†Travenol Laboratory, Incorporated, Morton Grove, Ill.
‡Courtesy of Hal Berlin and Kenneth Woodward, Diamond Ordnance Laboratory, Washington, D. C.

Table I

	No. of dogs	Hours	B.P. control (mm. Hg)	B.P. bypass (mm. Hg)	Flow (c.c./min.)	Flow (c.c./kg./min.)	Hct. control	Hct. dur. bypass	Plas. hgb.	Survival	Transfusions: Blood	Transfusions: Nonblood
Avg.	6	10	143	113	1,099	51	52	35	102.3	3	1,540 c.c.	810 c.c.
Range			120-160	90-150	931-1,[illegible]	41-58	41-72	29-40	85-325		154 c.c./hr	81 c.c./hr
Avg.	5	6	136	91	745	33	43	32	81	0	1,900 c.c.	1,160 c.c.
Range			80-180	40-160	200-1,300	[illegible]-35	41-4[illegible]	30-31	[illegible]-140		310 c.c./hr	193 c.c./hr

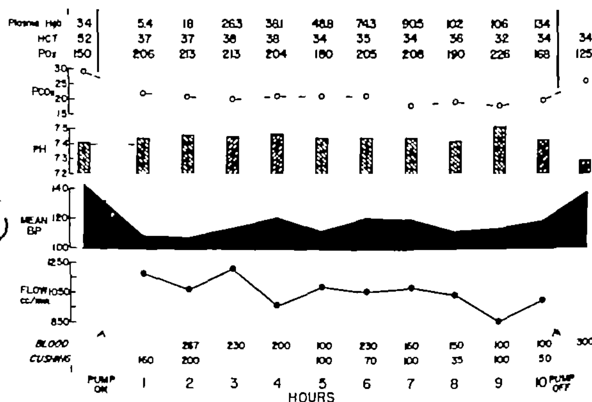


Fig. 1. Ten-hour partial bypass in dogs with bubble oxygenator and Army pump. Progressive hemolysis, sequestration acidosis, and decline in blood pressure and flow were characteristic of all dogs.

of the experiment. Hourly urine output was determined by a suprapubic or urethral catheter in the bladder.

Results

Ten-hour bypass. Six dogs were placed on partial jugular vein to femoral artery bypass for ten hours. Flows varied from 41 to 58 c.c. per kilogram per minute with an average of 51 c.c. per kilogram per minute—approximately half the mean cardiac output of a similar group of anesthetized dogs. Blood pressure during bypass averaged 113 mm. Hg in contrast to mean blood levels of 143 mm. Hg prior to bypass (Table I). Hematocrit during bypass was maintained between 29 and 40 per cent (mean 35 per cent) by transfusions of Ringer's solution or blood. Plasma hemoglobin rose steadily during bypass to

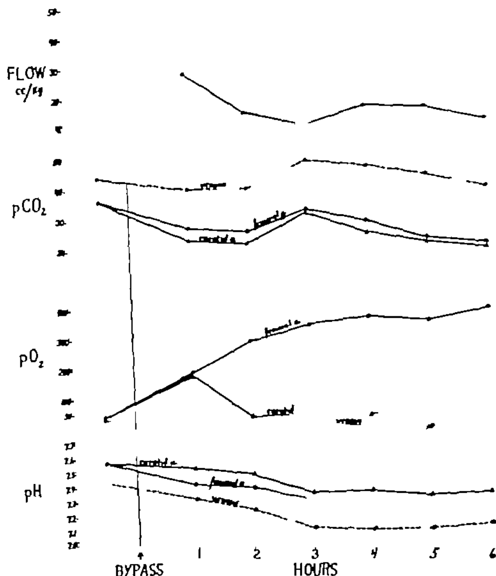


Fig. 2. Six-hour bypass showing the discrepancy between carotid and femoral oxygen tensions when on partial bypass. Brain and heart perfusion are determined by the cardiac output and not the pump return. The changed pH and extracorporeal flow are similar to those in ten-hour partial perfusions.

levels between 85 and 325 mg. per cent at the end of bypass. The reason for this variation is not clear. It was not related to the amount of extracorporeal bypass flow.

Transfusions in 200 c.c. amounts were given more frequently as bypass progressed to maintain initial flow and blood pressure levels. In spite of this, there was a gradual decline in the blood pressure and flow as perfusion continued (Fig. 1). An average of 1,540 c.c. (154 c.c. per hour) of blood and 810 c.c. of Ringer's solution (81 c.c. per hour) was given for each ten-hour experiment.

Three dogs were long-term survivors (50 per cent). The remaining dogs died immediately following bypass or within a few hours of its cessation in pulmonary edema and shock.

Serial pH and pCO_2 determinations revealed progressive metabolic acidosis

during perfusion that was corrected by 44 to 88 mEq. of $NaHCO_3$ five hours after the start. Respiratory alkalosis was present throughout the procedure. pCO₂ varied between 12 and 35 mm. Hg with an average of 20 mm. Hg. pH averaged 7.36 for the bypass time and was observed to drop as low as 7.29. Partial pressure of O_2 in the femoral artery varied from 71 to 410 mm. Hg, a reflection of the variation of flow and the limited capacity of the oxygenator.

Six hour bypass. In five dogs, the bladder was catheterized via the urethra or transperitoneally for measurement of urine output. The additional procedures, though small, contributed to additional blood loss and resulted in smaller flows and a more marked reduction of mean blood pressure for the period of bypass. Transfusions of

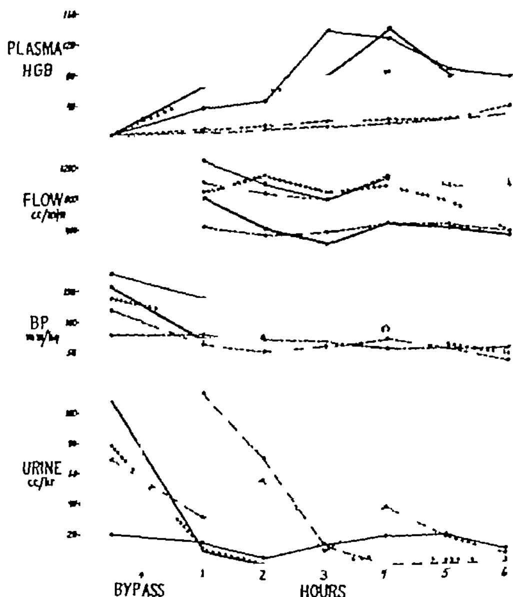


Fig. 3. Six hour bypass experiment showing the marked reduction in urine output within the first three hours despite small changes in mean blood pressure and extracorporeal flow. A corresponding rise in plasma hemoglobin occurred though it is not known whether this is related to the changes in urine output.

blood averaged 1,860 c.c. per experiment or 310 c.c. per hour (Table I). This was over twice the rate required during the ten-hour bypass with its small incisions and limited amount of surgical blood loss and was directly responsible for limiting the bypass time to six hours. Extracorporeal flows averaged 748 c.c. per minute or 33 c.c. per kilogram per minute. Blood pressure during bypass averaged 45 mm. Hg below the control level in spite of the increased transfusion rate. Metabolic acidosis was evident in all and increased as perfusion progressed (Fig. 2). Control pH 7.49 with normal pCO_2 fell to 7.45 with bypass and 7.33 at the end of bypass, in spite of respiratory alkalosis and sodium bicarbonate. Prior to bypass, pCO_2 was in the normal range of 39 mm. Hg. During bypass, pCO_2 varied from 21 to 30 mm. Hg and averaged 25.6 mm. Hg. Hematocrit averaged 3[illegible] per cent. Carotid artery pO_2 averaged 57 mm. Hg and reflected ventilation of lungs with room air. A marked discrepancy existed between the oxygen tension of femoral blood representing return from the oxygenator and carotid samples representing blood returning from the lungs (Fig. 2). This represents a potential disadvantage of this system if there exists a defect in the oxygenating capacity of the lungs since desaturated blood will then perfuse the heart and brain unless total cardiac return is diverted to the pump oxygenator.

Hourly urine output was markedly reduced after two hours of bypass. All dogs were anuric by the end of the procedure. Three were anuric by the third hour of bypass. Diuresis was noted immediately after discontinuing bypass. The change in urine output paralleled the rise in plasma hemoglobin (Fig. 3).

Discussion

The data of this study indicates that partial venous-arterial bypass diverting approximately 50 per cent of the cardiac output to an extracorporeal system containing a bubble oxygenator and the pulsatile Army pump cannot be used safely for periods as long as ten hours. Normal hemodynamics are not maintained, acidosis is progressive, kidney function is markedly depressed, sequestration and hemolysis continue without diminution during the period of bypass. This discrepancy that exists between the oxygen content of the blood returning from the lungs to the heart and that being returned to the lower body by the extracorporeal system becomes important since the heart and brain may be perfused by a poorly saturated pulmonary return. The brain however is not exposed to dangerous levels of pO_2 while on this type of partial bypass.

The sequelae of blood trauma incident to venoarterial bypass are acidosis, pulmonary damage,[2] sequestration, renal dysfunction, vasoactive agents, and coagulation defects. The degree of such changes are apparently related to the minute flow and the portion of the cardiac output that is diverted. Hopf and associates reported results using bypass flows of 600 ml. per minute (36.3 ml. per minute per kilogram or approximately 42 per cent of the cardiac output) for ten-hour periods. Of 38 dogs 25 were long-term survivors. Hemolysis, leukocytosis, increased mechanical fragility of the red cells, expansion of the extracellular fluid compartment, and a postperfusion anemia were prominent findings. Animals perfused with a membrane oxygenator had a significantly higher urinary output then those perfused with a bubble or disk oxygenator. Plasma hemoglobin remains the best quantitative criterion of blood trauma during bypass. Neville and associates[3] found a strong correlation between the development of a postperfusion pulmonary vasculitis and the plasma hemoglobin levels; the leukocyte response was absent below 50 mg. per cent and minimal when a membrane oxygenator was used.

The importance of pulsatile versus a mean pressure flow is still undecided. The magnitude of the changes effected by most oxygenators tends to obscure the effect of how the blood is returned to the body or whether normal pulsatile flow is ideal for prolonged perfusions. There is evidence that indicates improved lymphatic return, reduction of edema, sequestration of blood, arteriovenous shunts,[12] and prevention of release of potent vasoconstrictor agents from the kidney with pulsatile flow.[13]

Summary

Six hour and ten hour partial veno-arterial bypass studies were performed with the use of the disposable bubble oxygenator and the Army artificial heart pump Progressive hemolysis, sequestration acidosis hypotension and decreased renal function were observed as the bypass continued

REFERENCES

1 Kresna, J H Shuster M Baens, H Kreel, I and Baronofsky I D Study of acid-base and electrolyte derangement after prolonged cardiopulmonary bypass, J Thoracic & Cardiov Surg 42:244 1961
2 Kirklin J W Pulmonary dysfunction after open heart surgery M Cl North America 48 1063 1964
3 Neville W E Loutaxes, A Ga n T and Clowes, G H A J Postperfusion pulmonary venulitis, Arch Surg 86 126 1963
4 Litwak, R S Slonim, R Wisoff B G and Gadboys, H L Homologous blood syndrome during extracorporeal circulation in man II Phenomena of sequestration and desequestration, New England J Med 268 1377 1963
5 Clene J G Weedman, W H Weklm, K C Roses ar J W Kirklin, J W and Stickler C B Renal function and hydrogen-ion excretion after open intracardiac surgery and whole body perfusion, Ann Surg 157:336, 1963
6. Hollenberg M Pruett R and Thal, A P Vasoactive substances liberated by prolonged bubble oxygenation J Thoracic & Cardiovas Surg 45 102, 1963
7 C s, H Lillehei C. W and Krivit, W Problems in hemostasis during open heart surgery I On the release of plasminogen activator Ann Surg 154:915 1961
8 Hopf M A Brinsfield, D E, Martinez F J and Galletti, P M Laboratory experience with long lasting perfusion, Tr Am Soc Artif Int Org ns 8:57 1962
9 Brinsfield, D E Hopf M A, Meyer S E, and Galletti, P M Body fluids and electrolytes after prolonged cardiopulmonary bypass, J Appl Physiol 19:566, 1964
10. Parsons, R J and McMaster P D Effect of pulse upon the formation and flow of lymph, J Exper Med 68 353, 1938
11 Nakayama K Tamiya, T Yamamoto, K Izumi, T Akimoto, S, Hashizume S Iimori, T Odaka, M and Yazawa, C High amplitude pulsatile pump in extracorporeal circulation with particular reference to hemodynamics, Surgery 54 798, 1963
12 Ogata, T Ida, Y Honoyama, A Takeda, J and Sasaki H A comparative study of the effectiveness of pulsatile and non-pulsatile blood flow in extracorporeal circulation, Arch Jap Chir 29:59 1960
13 Harris J S. Selby W C and DeMaria, W Hypertension and renal dynamics in aortic coarctation, Am. J Med 9 731 1950
14 Tobian, L The relationship of the juxtaglomerular apparatus to renin and angiotensin, Circulation 25 189 1962

Case reports

An intermittent 'cooing' diastolic murmur due to a torn aortic valve cusp

*Gerald F. Fletcher, M.D.**
*J. Willis Hurst, M.D.***
Atlanta, Ga.

Whenever the diastolic murmur of aortic regurgitation has a "cooing" musical quality, it is proper to consider an unusual cause for the disorder. Such a murmur may be due to retroversion of an aortic valve cusp secondary to syphilitic aortitis, prolapse of an aortic valve cusp associated with dissecting aortic aneurysm, fenestration of an aortic valve cusp due to bacterial endocarditis, or be related to the coalescence of congenital lacuna of the aortic valve or abnormality of the aortic valve due to trauma.[1-4]

As a rule, the murmur has a pure musical tone and is present with each heart cycle. The purpose of this report is to describe a patient who had an *inconstant* "cooing" diastolic murmur superimposed upon the constant murmur of typical aortic regurgitation.

The patient described in this report had mild systemic hypertension, history of treated syphilis, positive fluorescent treponema antibody reaction, and a peculiar tear in an aortic valve cusp. The musical murmur simulated the murmur associated with retroversion of an aortic valve cusp. The murmur varied from being quite loud during one heart cycle to being inaudible a few heartbeats later. The murmur was audible to the patient and this caused him considerable anxiety.

Case report

A 56-year-old Negro man was referred to Grady Memorial Hospital on Nov. 13, 1966, because his physician had noted a dramatic change in his heart murmur. The patient's major complaint was "I hear a noise in my heart." The patient could indicate when he heard the noise by briskly moving his finger. (His finger movement proved to be synchronous with the intermittent diastolic murmur heard during physical examination.)

The patient had been treated for syphilis 20 years prior to referral (gluteal injections). He had received intermittent treatment for mild systemic hypertension which had been present for many years. The typical murmur of aortic regurgitation had been heard by his physician for three years, but the new inconstant diastolic murmur had been heard for only several weeks. There was no history of chest trauma or strenuous effort.

The systolic blood pressure was 190 mm. Hg and the diastolic pressure was 90 mm. Hg. The neck veins were slightly engorged and a rapid upstroke was noted in the carotid pulsations. Fine râles were heard in each of the lung bases. The apex impulse of the heart was abnormally large and laterally displaced. The atrial contribution to the apical movement was easily felt in the presystolic period. A loud (Grade 4 on the scale of 6) high-pitched decrescendic diastolic murmur of aortic regurgitation was heard along the left sternal border. A

From the Department of Medicine, Emory University School of Medicine and the Medical Service of Grady Memorial Hospital, Atlanta, Ga.
Received for publication May 12, 1967.
*Fellow in Department of Medicine (Cardiology), Emory University School of Medicine.
**Professor and Chairman, Department of Medicine, Emory University School of Medicine and Chief of the Medical Service, Grady Memorial Hospital.



Fig 1 Phono rd g m show ng the loud cooing diastolic murmur of aortic regurgitation Note the *inter mittent* o rene of he m urmur nd the change the murmur from cycle to cycle (Line one is the ECG re orded n l ad I l ne tw how the hanging dia tolic murmur recorded in the second left interspac near the t rnal l rder

extremel loud (Grad 5 in sc le of 6) high-pit hed m ical ooing dia olic murmur w heard periodic lly and w superimposed upon the typic l murm of aort regurgit tion (Fig 1) A Grade t il murmur was heard t the upper left ternal border nd Grade pic l diastol rumble w roduced by loud entricular gallop A trial sound w lso he rd The li er was lightl enlarged All peripheral arterial pulses were forcef l th pad pitrok Venous aric es were presen the right lower leg

R ne complet blood ou t nal is blood ure trogen blood sugar nd serum electroly t normal A nereal dise se research laboratory ser logic t t for ph l negat e on t oc sions The fl rescent reponem antib dy absorp test positiv A lect ocardiog am (ECG) showed lef entricular hypertroph with entricu la t ypa he ts A chest r y rev led ardiac enlarg t (left ventricle) with tortuosity of the thorac aor N lc fic tion ould be seen he aort root

Cardiac heter tion was performed on Nov 14 1966 th passage of Gens catheter per utaneousl through the right femoral artery The aort c s olic pressure w 200 mm Hg nd the dia tol pressure was 70 mm Hg An aortogram following n jection of ont ast solution 2 cc bov he aort h showed what was interpreted to be moder te to severe aortic regurgitation. It w not possible to identify peculiar abnormality of the ort al usps Because of technical diffic lty d ancement of the catheter the left entricle was not entered

The physical findings were felt to be indicativ of congestiv heart failure and he w placed on digitalis. During the next several weeks of observ tion, it became obvious that the patient limited his activity l order t oid symptoms. Surgical tre t ment of the aortic lv was uggested because of the degree of aortic regurgitation the signs of heart failure, the noise heard by the patient, and because retroversion or prolapse of an aortic valve cusp is likely to lead to progressiv heart failure

Surgery on the aortic val was performed by Dr Peter Symbas of the Department of Surgery of Emory Universit School of Medicine on Jan. 25 1967 At the time of surgery the aorta ap peared normal except for prominence of the also vasora. There wa no excessiv dilatation or intimal changes. There was 5 mm. tangential tear of the left aortic cusp adjacent to the posterior cusp. The aortic cusp, except for the tear appeared normal. The aortic valve was resected and a number ten Starr Edward prosthetic ball alv as inserted The hist logic examination of the exc sed aortic alv cusps wa normal except for the tear

Postoper t el the patient had complication of pneumonia and infection t the sit where ut enou catheter had been placed for the pur pose of monitoring the central enous pressure At the time of discharge there considerable im provement of h cardiac status

Examination of the patient eight week after surgery revealed les linical evidence of left en tric lar enlargement nd no overt evidence of con gesti heart f ilure The blood pressure as 140 mm Hg systolic and 90 mm. Hg diastolic The me hanical lick of the prosthetic alv ere audible to the exam ner but not by the patient A Grade 2 systolic murmur was he rd t the mid-lef sternal l rder There was no murmur of aortic regurgit tion

Discussion

The unusual feature of this case is that the loud cooing diastolic murmur oc curred *intermittently* and was superimposed upon the typical murmur of aortic regurgi tation The cause of the murmur in this case was an unexplained tear in the left aortic cusp It seems likely however that the torn aortic cusp would become retro verted or would prolapse in an intermittent fashion

The cause of the *intermittent* dysfunction of the valve could not be found There was no relationship of the murmur to normal respiration The Valsalva maneuver did not alter the occurrence of the murmur Stren uous exercise did not change the ausculta tory events and sublingual nitroglycerine did not alter the occurrence of the murmur

Summary

We have reported a patient with an ex tremely loud cooing diastolic murmur of aorta regurgitation that occurred *inter mittently* The murmur was periodically superimposed upon the typical murmur of aortic regurgitation and was similar to the murmur associated with retroversion of an

aortic valve cusp. The unusual murmur varied greatly from heart cycle to heart cycle and within a few heartbeats would range in intensity from very loud to inaudible. The murmur was secondary to a 5 mm. tear in the left aortic cusp although, in addition, the patient had a history of treated syphilis and mild systemic hypertension. The cause of the *intermittency* of the murmur and probable retroversion or prolapse of the cusp was not determined. Aortic valve surgery was recommended and executed because the aortic regurgitation was severe and presumably progressive, because heart failure was noted on physical examination, and because the intermittent murmur was audible to the patient.

REFERENCES

1. McKusick, V. A.: Cardiovascular sound in health and disease, Baltimore, 1958, The Williams & Wilkins Company, pp. 3, 16, and 269.
2. Bellet, S., Gouley, B., Nichols, C. F., and McMillan, T. M.: Loud musical diastolic murmurs of aortic insufficiency, AM. HEART J. 18:483, 1939.
3. Gelfand, D., and Bellet, S.: The musical murmur of aortic insufficiency: clinical manifestations based on study of 18 cases, Am. J. M. Sc. 221:644, 1951.
4. Steinbridge, V. A., Hejtmancik, M. R., and Herrmann, G. R.: Unusual musical murmurs of anterior cusp aortic regurgitation: report of ten cases, AM. HEART J. 48:163, 1954.

Supravalvular pulmonic stenosis, abnormal facial appearance, and mental retardation

Gottfried Hartel M D *
M Heikki Frick M D
Pentti I H lonen M D
Hel inki Finland

Williams and associates[1] first de scribed four patients with supra lvular aortic stenosis, peculiar facial appearance and mental retardation The association of these findings is now well recognized as a syndrome -4 This report is concerned with sim'lar findings in a patient in whom the supravalvular stenosis was immediat ly distal to the pulmonary valves.

Case report

A girl, 15 ears of age w adm tted t the U iversity Central Hospital in 1964 She amo from fam l of six hildren and w the third-born hild Her mother was w ll during the pregnancy nd did not tak my itamin supplements There as no relevant family history The baby was t The twi brother was dead t birth and had supposedly died about one month earlier The girl w born at full term. Her face was peculiar from the begi ing nd she was slow in ll aspects of her development. At the age of six she started t complain bout effort dyspnea nd precordial pal on exertion. A basal systolic murmur was found. Her exercise tolerance has not changed since. She was poor student at lementary school nd stayed back year I the first grade According to her mother she has al y been without i itatl and is easily frightened.

Examination at the ag of 15 revealed a aby girl with obvious mental retardation. Her height as 153 cm. her weight was 46 5 kilograms. She had a characteristic face w th broad depressed nasal ridge coarse pouting lips prognathism nd re ceding hi (Figs. 1 nd 2). The upper canine teeth had been extract d t the age of 14 There w slight onecom tant t abismus of the left eye The excess pressure appeared normal, but the as was conspicuou Sustained parasternal lift suggested right entricular hypertrophy the apex beat wa palpable. A Grade 4/6 ejection-t pe stolic rmur was ma imal in the left second and third intercostal paces nd was accompanied by systolic thrill The second heart sound was clearly split t the left ternal border The splitting widened w th in-pira tion No ejection sound or diastolic murmur was heard. The blood pressure was 130/80 mm. Hg The lectrocardiogram showed right is deviation (AQRS +145°) and both right atrial nd right ventricular hypertrophy A chest radiogr ph showed normal heart olume (340 ml. per square meter of body surface) and a lightly prominent right en tricle The lung ascularity was normal

Right cardiac theterization was carried out in June 1964 The pressures recorded (in millimeters of mercury) were 14/8 in the right pulmonary artery nd in the main pulmonary artery 49/10 imme diately bo e the pulmonary valves, and 50/0-5 in the right entricle. Femoral arterial pressure as 128/66 There was no evidence of shu ting from the oxygen saturations or dye dilution curves. Angiocardiography with injection of the contrast medium int the right entricle revealed a suprav aly lar pulmonary stenosis caused by membrane immediately distal t th al es (Figs. 3 and 4) Post tenotic dilat tion of the mai pulmonary artery was obvious. Aortography howed normal aortic root (Fig 5).

The results of other investigations ere as follow The I Q was 83 Buccal smear showed hromatin positi cells nd the hromosomes l the periphera-

Received for publication M y 22, 1967
*First Medical Department Universit Central Hospital, Helsinki 29 Finland.



Fig. 1. Patient at 17 years of age.

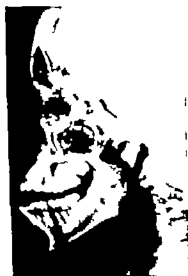


Fig. 2. X-ray film of the skull showing prognathism and receding chin.

leukocytes were normal. The hemoglobin was 14 Gm. per 100 ml. The blood group was B, Rh positive. Serum calcium was 10.1 mg. per 100 ml. and serum phosphorus 4.6 mg. per 100 ml. Protein-bound iodine 7.0 μg per 100 ml., and serum cholesterol was 213 mg. per 100 ml. Serum protein was 7.0 Gm. per 100 ml. and the fractionation by paper electrophoresis showed a normal pattern. Serological tests for syphilis were negative. Renal function and the amino acid excretion in the urine were normal. Radiographs of the bones did not reveal any further abnormalities. The retinal vessels were normal.

Discussion

During the past decade postvalvular stenosis of the pulmonary artery and its branches has become a well known anomaly due to the introduction of cardiac catheterization and selective angiography. Bell and associates reported 14 cases among 175 patients with congenital heart disease. Agustsson and co-workers found 60 cases with bilateral multiple stenosis of the pulmonary artery in a series of 1,650 cardiac catheterizations. In 1964 Oram and associates surveyed the earlier literature and found 202 patients reported who had postvalvular stenosis of the pulmonary artery and its branches. The authors analyzed 108 cases, where adequate descriptions of clinical features and investigations were given, and added details of a further nine patients of their own. Of the 117 cases, 49 patients had multiple peripheral stenoses with or without stenosis of the right or left main branch (Type I), 49 had stenosis at the bifurcation of the pulmonary trunk (Type II), and 11 had stenosis of the pulmonary trunk (Type III). A further eight patients had combinations of these three types. Postvalvular pulmonic stenosis, when proximal to the bifurcation of the main pulmonary artery, usually extends over a short segment and forms a coarctation of the pulmonary artery.

The patient described in this report had a supravalvular stenosis of the pulmonary trunk due to a membranous septumlike constriction about 1.5 cm. distal to the pulmonary valve. This type of postvalvular pulmonic stenosis seems to be rare.[-13]

Postvalvular stenosis of the pulmonary artery is often associated with other congenital abnormalities, both cardiac and noncardiac. This holds true also in patients with supravalvular pulmonic stenosis due to a septumlike membrane. The associated cardiovascular lesions have included stenosis of the pulmonary valve and of the right branch of the pulmonary artery, multiple peripheral stenosis of the pulmonary artery[11] and supravalvular aortic stenosis.[11,13] The present case had none of these anomalies. There were, however, additional noncardiac features—a peculiar facial appearance and mental retardation—known to occur as charac-



Fig 3 Right entricula ngiocardiogram (l t le) Pulmonary cusps ere intact They opened nd losed normally



Fig 4 Right entricular angiocardiogram (early diastole) revealing septumlik membrane about 1 5 cm distal t the pulmonary lve nd post stenotic dilatation of the pulmonary artery

t ristic parts of a syndrome in patients with supravalvular aortic stenosis.

The syndrome of supravalvular aortic stenosis was first described by Williams and associates in fou unrelated children The ch ldren showed a striking facial resemblance derived largely from soft tissue similarities. They had full faces with broad foreheads, heavy cheeks wide mouths and pointed chins. The eyes were well apart and some had pouting lips malocclusion of the teeth and prominent ears. All of them were mentally deficient and had supravalvular aortic stenosis.

Subsequently a number of cases have been published displaying a wide variety of additional clin cal manifestations association of postvalvular pulmonic stenoses,[2 14] certain dental malformations, and narrowing or tortuosity of the retinal vessels.[1] The relationship of the syn drome with idiopathic hypercalcemia was documented by Garcia and associates.[1] With one exception[7,18] patients with the complete syndrome were found to have normal chromosomes.[13 21] On the basis of family studies, Merritt and co-workers[14] proposed two groups of patients with supravalvular aortic stenosis (1) sporadic



Fig 5 Aortography showing normal aortic root

cases with the complete syndrome (2) familial cases without mental retardation and facial similarity Logan and associates[22] suggested a similar classification including the following types (1) supra valvular aortic stenosis with normal facial

appearance and intelligence either (a) familial or (b) nonfamilial sporadic (2) syndrome of supravalvular aortic stenosis with abnormal facial appearance and mental retardation, with (a) normal chromosomes and occasional association with severe infantile hypercalcemia or multiple pulmonary artery stenoses, or (b) abnormal chromosomes.

Actually postvalvular pulmonic stenosis may be associated with all types of supravalvular aortic stenosis. Its occurrence has also been reported in patients with isolated nonfamilial supravalvular aortic stenosis[26] and in patients with isolated familial supravalvular aortic stenosis.[7] Among ten cases with the syndrome of supravalvular aortic stenosis, Blanquaert and associates[27] reported two cases with additional supravalvular pulmonic stenosis. Because of the abnormal facial appearance and mental retardation the present case with supravalvular pulmonic stenosis alone may be regarded as a variant of the supravalvular aortic stenosis syndrome not previously described. Other features in common with that syndrome were the nonfamilial occurrence, normal chromosomes, and malocclusion of the teeth. No signs of hypercalcemia were detectable in this case and there were no further stenoses of the pulmonary vascular tree.

Supravalvular aortic stenosis and its accompanying lesions are considered to be of congenital origin. Because of the similarity between the facies of children with the complete syndrome and the facies of children surviving idiopathic hypercalcemia in infancy, a connection between these two diseases was suggested.[28] This relationship was confirmed by cases displaying both abnormalities.[3,4] Antia and co-workers[17] suggested that hypercalcemia might be important in all patients with supravalvular aortic stenosis. Beuren and associates[21] consider vitamin D application or vitamin D sensitivity an important etiological factor in supravalvular aortic stenosis, as well as in coexisting hypoplasia of the aorta and of the pulmonary artery. Experimental studies in animals have confirmed that aortic lesions similar anatomically to supravalvular aortic stenosis in man can be produced in the offspring of rabbits receiving large doses of vitamin D during pregnancy.[29]

Besides idiopathic hypercalcemia and vitamin-D overdosage, maternal infection during pregnancy has to be considered as a possible cause of postvalvular pulmonic stenosis. Maternal rubella is an established cause of fetal malformations of the cardiovascular system.[30-32] In several cases of postvalvular pulmonic stenosis, the mother had rubella during the early months of pregnancy.[31,33] Rowe[33] described 11 patients with a history of maternal rubella, nine of whom had bilateral pulmonary artery stenosis, and suggested that rubella may be an important etiological agent in pulmonary artery stenosis. This view is supported by Venables,[34] who found bilateral pulmonary artery stenosis in five children following maternal rubella during pregnancy.

There also seems to be a familial factor in isolated postvalvular pulmonic stenosis, since the disease has been reported in siblings.[26]

The present case does not offer any etiological clues. The malformation was certainly congenital and the intrauterine death of the twin brother was possibly caused by even more severe congenital lesions; however, no additional information was available.

Summary

A case of supravalvular pulmonic stenosis in a mentally retarded girl is described. She had a peculiar face and malocclusion of the teeth. A possible relationship with the syndrome of supravalvular aortic stenosis, characteristic facies, and mental retardation is discussed.

REFERENCES

1. Williams, J. C. P., Barratt-Boyes, B. G., and Lowe, J. B.: Supravalvular aortic stenosis, Circulation 24: 1311, 1961.
2. Beuren, A. J., Apitz, J., and Harmjanz, D.: Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance, Circulation 26: 1235, 1962.
3. Black, J. A., and Bonham Carter, R. E.: Association between aortic stenosis and facies of severe infantile hypercalcaemia, Lancet 2: 745, 1963.
4. Beuren, A. J., Schulze, C., Eberle, P., Harmjanz, D., and Apitz, J.: The syndrome of supravalvular aortic stenosis, peripheral pu

stenosis ment l retardation, nd similar facial ppear nc A J Cardiol 13:471 1964
5 Williamson D A J Supr lvar aortic tenosis sso ted with mental nd ph sical retard t on nd haracteristic facies, Proc. Roy Soc Med 3 118, 1964
6 Bell A l l J Kughtlinger B Shimomura, S nd Kirst kovic A Postvalvular pulmonary rtery stes is hemod namic and radiogr phic defi t on, Circulation 26:683 1962
7 Ag sson M H Arcilla R A Gas l, B M B off J P N saf S l nd Lendrum B L The diagnosis of bilater l tenosis of the primary pulmonary rtery branches based on characterist pulmonary tru k pressure curves A hemodynamic nd angiocardiogr phic stud Circ lation 26:421 1962
8 Or m S P ttinson A nd D ies, P Post valvula stenosis of the pulmonary artery and t branches, Brit Heart J 26:832 1964
9 (llensw rd A Lodin H Lundberg L and Moller T *Congenital m ltiple peripheral* tenoses of the pulmonary artery Pediatrics 19 499 1957
10 Kjellberg, S R Mannheimer E Rudhe l d Jonsson, B *D gnos of congenit l heart* disease ed 2 Chicago, 1959 Year Book l blisher Inc p. 221
11 Arvid son H Carlsson, E H rtma n, L J Fal ths, A and Crawford, C Supra afvula stenoses of the pulmonary arteries Report of ele en es, Acta radiol (Stockholm) 56:166, 1961
12 W tson, G H Supra alvar pulmonary nd ortic tenoses coexisting Brit Heart J 25:817 1963
13 Blancquaert, A D puis, C Hooft C Nuyts, J P nd P nner R. Stenoses pulmonaires et aortiques postvalvulaires vec facies pa ticulier et retard intellectuel, Act cardiol. 21:611 1966
14 F J E Lynn, R. B nd Partington, M W Supr alvular aortic stenosis, mental retardation, and characteristic facies, Canad M A J 93:295 1965
15 Myers, A R and Willis, P W Clinical spectrum of supravalvular aortic tenosis, Arch. Int. Med 118:553, 1966
16. Garcia, R. E Friedman, W F Kaback, M M nd Row R. D Idiopathic hypercalcemia nd supravalvula aortic stenosis, New England J Med. 271 117 1964
17 Palmer C. G *Chromosome studies in patient* with supravalvular aortic stenosis, Lancet 2 788, 1963.
18. Merritt A. D P lmer C. G Lurie P R and Petry E. L. *Supravalvar aortic tenosis* Genetic nd clinical studies, J Lab & Clin. Med. 62:995 1963.
19 Eberle, l nd Beuren A. J Chromosome tudies l patient with supravalvular aortic tenosis, Lancet 2 438 1963.
20. Joseph M C Polani, P E and Gold R. G: Chromosome studies in patients with supra valv lar aortic tenosis, Lancet 2 788, 1963.
21 De Grouchy J and Emerit, l Chromosome studies *in* patient with supravalvular aortic tenosis, Lancet 2 789 1963
22 Logan, W F W E., Jones, F W W lker E., Coul hed A and Epstein, E. J F milial supra lva aortic stenosis, Brit. Heart J 27:547 1965.
23. Bourassa, M G nd Campeau, L. Combined supra alvular aortic and pulmonic stenosis, Circulation 28:572 1963.
24 K hler R L., Braunwald E., Pla th, W H Jr nd *Morrow* A. G Familial congenital heart d ease Am J Med. 40:384 1966
25 Hooft C Vermassen, A nd Blancquaert A. Observations concerning the evolution of the *hronic form of idiopathic hypercalcaemia in* hildren, Helvet. paediat. acta 18 138, 1963
26. Joe K. L Voren G R., and Anderson, R. C. The syndrome of idiopathic hypercalcemia of *infancy* with associated congenital heart dis ease J Pediat. 67 1130 1965.
27 A tia A. l Row R D Otteson O E., Levin, S nd Cooke R E Pathogenesis of the supra lvular aortic stenosis yndrome in ch'ldren, Circulation (Suppl 2) 32:44 1965
28 Beuren A. J Apitz, J Stoermer J Schlange H Kaiser B v Berg W and Jürgensen, G. Vitamin-D-hypercalcämische Herz nd Gefässerkrank ng Deutsch. med. Wchnschr 91:881 1966.
29 Friedman, W F nd Roberts W C. Vitamin D nd the supr valvar aortic stenosis syndrome the transplacental effect of vitamin D on the ort of the rabbit, Circulation 34 77 1966.
30. Pitt, D B Congenital malformations and maternal rubella Progress report M J Austr lia 18:881 1961
31 Higgins, G C and Phillips, L I: Rubella embryopathy Brit. M J 1 711 1963.
32 Campbell, M Place of maternal rubella in the aetiology of congenital heart disease, Brit. M J 1:691 1961
33 Row R. D M ternal rubella nd pulmonary artery stenoses Report of eleven cases, Pediatrics 32 180, 1963.
34 Venables, A. W The syndrome of pulmonary stenosis complicat ng maternal rubella, Brit. Heart J 27:49 1965
35 V n Epps, E. F Primary pulmonary hypertension in brothers, Am. J Roentgenol. 78:471 1957

Clinical pathologic conference

Giuseppe G. Pietra, M.D.
Earl Silber, M.D.
Bertram Levin, M.D.
Alfred Pick, M.D.
Chicago, Ill.

Presentation of case

A 59-year-old Negro man was admitted to the Michael Reese Hospital and Medical Center on Sept. 30, 1966, because of chest pain.

He had been well until January 1966 when he began to experience left-sided chest pain associated with shortness of breath. In February 1966 the pain changed to the right side and was associated with cough. A chest x-ray showed right bronchopneumonia and cardiomegaly. He was hospitalized elsewhere and treated with antibiotics, digitalis, and diuretics with resolution of the pneumonia. The shortness of breath, left chest pain, weakness, and occasional palpitations persisted. Ankle edema appeared in April, 1966, and he has been unable to work since that time. The left-sided chest pain became moderately severe, was stabbing in nature and aggravated by respiration. He had lost approximately 20 pounds since the onset of his illness.

Physical examination on admission revealed a cachectic Negro man in moderate respiratory distress with inspiratory retractions of intercostal muscles. His pulse was 64 per minute and blood pressure was 110/80 mm. Hg. Respiratory rate was 22 per minute and regular. The eyegrounds showed arterial narrowing and A-V nicking. The neck veins were filled to the angle of the mandible at 30° elevation. There was palpable pleural friction rub over the left midposterior axillary region.

The left hemithorax was splinted and the lower half was dull to percussion; breath sounds were decreased or absent in this area. A diffuse apical pulse was palpated in the sixth intercostal space at the anterior axillary line. There was a left parasternal lift. The first and second sounds were loud. There was a Grade II/VI systolic ejection murmur at the base and lower left sternal border. No pulses were felt below the femorals bilaterally. Total liver dullness measured 13 cm. A positive hepatojugular reflex was present. There was 4+ pitting edema peripherally. A chest film revealed extensive left pleural effusion occupying two-thirds of the left hemithorax and blunting of the right costophrenic angle. The electrocardiogram (ECG) revealed sinus rhythm with incomplete A-V dissociation and shifting of the pacemaker. Hemoglobin was 12.9 Gm. per cent, hematocrit, 42 per cent. White blood cell count was 10,800 per cubic millimeter with 68 per cent segmented neutrophils, 9 per cent nonsegmented neutrophils, 8 per cent lymphocytes, 11 per cent monocytes, 2 per cent metamyelocytes, and 2 per cent myelocytes. Prothrombin time was 15.8 seconds; partial thromboplastin time was normal. Blood sugar was 132 mg. per cent, blood urea nitrogen was 34 mg. per cent, and creatinine was 1.1 mg. per cent. Transaminases and serum lactic dehydrogenases were within normal limits. Alkaline phosphatase was 5.6 Bodansky units. Bilirubin was normal. Cephalin flocculation was 2+. Calcium was 9.3 mg. per cent and phosphorus 4.6 mg. per cent.

Thoracentesis yielded 800 c.c. of bloody fluid, containing 6 Gm. per cent of protein. Atypical mesothelial cells were present. Bronchoscopy revealed shift of the trachea and carina to the right. The bronchial orifices were normal on the right, but the left mainstem bronchus formed a sharp angle with the trachea, was narrowed about 2 cm. and was fixed. Bronchial washings and biopsy revealed no abnormal cells. A pleural biopsy revealed fragments of necrotic connective tissue, suggestive of connective tissue tumor. Mediastinoscopy revealed no enlarged lymph nodes and random biopsy of lymph node showed normal tissue. Tomograms of the left hilum revealed elevation of left mainstem bronchus with irregularity of the distal contours of the bronchus. Multiple sputum and bronchial washings were negative for acid-fast bacilli, fungi, and malignant cells. A first-strength PPD was positive at 48 hours. Skin tests for fungi were negative. A bone marrow examination was normal.

The patient's hospital course was characterized by progressive cachexia and increasing peripheral

From the Department of Pathology, Medicine, and Diagnostic Radiology and the Cardiovascular Institute, Michael Reese Hospital and Medical Center, Chicago, Ill.

edema. The left hemithorax remained dull. Digitalis and diuretics were administered without relieving his symptoms. He died on Oct 23 1966.

Differential diagnosis

DR SILBER As I read this protocol I came to the conclusion that we are dealing primarily with one of the less common forms of heart disease and that the results of laboratory tests were largely of value in telling us what diseases were not present rather than in establishing the correct diagnosis. Essentially the case is that of a 59-year-old man who by symptoms and from the description of the x rays, was apparently in intractable congestive heart failure a matter which is itself of some interest. He died presumably from this heart failure per se which is rare or more likely from a complication of long standing congestive heart failure. As one scrutinizes the data it is not possible to clearly implicate the common forms of heart disease in this man's illness. First he is not hypertensive second he has no obvious evidence either on auscultatory examination by x ray or from the pattern of the ECG to suggest a congenital cardiac lesion that is compatible with survival to the age of 59 and eventuates in heart failure. The description of his auscultatory findings provides no basis upon which to make a diagnosis of valvular heart disease. Finally unless one accepts the fact that the patient's age of 59 is sufficient in itself there is no real basis for a diagnosis of coronary artery heart disease. Therefore we are brought to the realm of the less common forms of heart disease.

I think we can deal with some of them with dispatch because his illness began with a pneumonia which resolved. Although many skin tests for fungi were done, they were quite unnecessary for such pneumonias do not spontaneously resolve and are rarely benefited by treatment a patient just does not get well if he has blastomycosis, aspergillosis or any of the other fungus diseases which are invariably fatal. If they do involve the heart the involvement is usually endocardial. This man clinically did not have such a disease.

Certainly in every patient with evidence of obscure heart disease, one must consider bacterial endocarditis but there is no basis for it here. In the first place, there is no mention of fever and we know that if a patient has bacterial endocarditis, fever is invariably noted if the temperature is carefully taken. In addition bacterial endocarditis does not produce intractable heart failure which dominates the clinical picture without evidence of endocardial involvement. So I think we need not be intimidated by the possibility of missing some uncommon etiologic type of bacterial endocarditis.

We come then to another possibility namely pericarditis. I think from the findings, one can be quite secure that this man did not have any important degree of pericarditis, although he might have had some hemodynamically unimportant effusion on the basis of passive congestion. If one reads the description of the heart, it is huge and hyperdynamic. There is a parasternal lift and an axillary impulse which is forceful neither of which is consistent with cardiac tamponade. Moreover this man does not present the clinical picture of cardiac tamponade and the electrocardiogram is strongly against a diagnosis of any type of chronic pericarditis. Therefore I am not concerned with the results of the tuberculin test because I do not think this man has any form of chronic cardiovascular type of tuberculosis or any other type of pericarditis effusive or constrictive.

One other entity that must be considered since I have said that the diagnosis lies in the realm of the exotic type of heart diseases, is the possibility that this man has some type of tumor metastatic or primary involving the heart. I think it can be said with some confidence that a tumor is not apt to be found. Metastatic involvement of the heart is not uncommon. It has been reported that 0.5 to 20 per cent of all carcinomas, depending upon how carefully autopsies are performed involve the heart by metastases. Almost invariably it is the pericardium which is involved. Rarely is the myocardium or endocardium affected. Metastatic involvement of the heart usually encases the heart with tumor or induces a pericardial effusion which produces a picture of pericardial constriction

Dr Earl Silber Attending Physician Department of Medicine.

or tamponade Two factors rule against metastatic involvement of the heart in this patient (1) the patient with malignant pericardial effusion is not apt to have survived as long as this patient did and (2) almost invariably a patient who had metastatic involvement of the heart has obvious evidence of metastases to the chest or elsewhere a situation not present here. In this patient a primary tumor was very carefully sought and none was found Four primary types of malignancy involve the heart in the majority of instances. Breast cancer is a common cause of metastases to the heart, second only to bronchogenic carcinoma. Next, in order of frequency are the lymphomatous diseases and finally melanoma The latter although an uncommon malignancy not infrequently metastasizes to the heart No evidence for any of these primary tumors is present. While there is hardly a primary tumor that has not produced a metastatic nodule in the pericardium if we dispose of these four major sources of tumor metastatic involvement of the heart is unlikely to be present.

DeSenac has said "The heart is an organ too noble to be attacked by a primary tumor Certainly primary tumors of the pericardium or of the myocardium are extremely rare Most of those of the myocardium occur in children and are rhabdomyomas or sarcomas. The common tumors which constitute about 75 per cent of primary neoplasms of the heart are the myxomas. Myxoma, which is an endocardial mainly left atrial lesion produces symptoms which are primarily those of obstructive rather than restrictive disease of the heart. They often mimic valvular disease, particularly mitral stenosis, except the course is much shorter and the findings are atypical and tend to fluctuate from time to time This is not the clinical picture of myxoma of the left atrium or really of any other chamber of the heart.

By default, one area of disease remains which is today not only fashionable but common. This is primary myocardial disease of the heart We have here so far as I am concerned a patient who has congestive heart failure without a demonstrable cause. The clinical picture fits that of primary myocardial disease in the sense that there is profound failure with of course cardiomegaly The findings on auscultation are not those of valvular disease they are



Fig. 1 Chest x-ray film taken on July 16 1966

consistent with congestive heart failure per se. I will touch upon the various etiologies of primary myocardial disease in a moment, but at this point, in order to feel a little more secure, I would like to see the x-rays. I would also like to see and hear about the ECG from Dr. Fick.

DR. LEVIN: The first film is one made prior to his admission to the hospital (Fig. 1). He was admitted on September 30; this film is from July 16. The frontal view shows marked cardiac enlargement and if I were to hazard a guess from this single film, I would favor that this is *marked left ventricular enlargement*, to the degree that I would wonder about aortic valve disease, although admittedly it would not be at all unusual to find hypertensive or arteriosclerotic heart disease. There is no evidence of abnormality of pulmonary vascularity. I make particular mention of this, because Dr. Silber wanted to rule out any congenital heart disease with left or right shunt. Whether or not there is anything in the left lung base that is obscured by the heart, whether pleural or pulmonary in origin, of course I do not know, but there is nothing otherwise to make me suspect that there is other than cardiac disease from just this single film. On the next film (Fig. 2A), which is the one made on the day of admission to the hospital, one can now see that the central shadow is much enlarged. There is evidence of pulmonary congestion as demonstrated by the hypervascularity on the right side, *and there is slight right pleural effusion* which even retrospectively was not seen on the film that I showed earlier. This massive left pleural effusion and slight right pleural effusion could be due to congestive heart failure, but we like to see the predominant effusion on the right in heart failure. However, depending on the state of the pleura, I suppose there may be more on the left than on the right. Perhaps

Dr. Bertram Levin, Chairman, Department of Diagnostic Radiology.



Fig. 2A. Chest x-ray film taken on Sept. 30, 1966.

pleural adhesions may prevent the greater accumulation on the right than on the left. Remember though that from just this film we cannot even be sure there is effusion on the left side

A lateral view made the same day did not help us at all It just shows a central big blob of white and how much is heart how much is lung and how much is pleura cannot be differentiated However the film made in a left lateral decubitus position (Fig 2B) shows that the fluid has layered along the left lateral chest wall showing there is marked left pleural effusion which was not definite from the frontal view Tomograms were made a week or two later (Fig 3) We see that there is marked deformity and irregular narrowing of the left main stem bronchus. The bronchus of the upper lobe is intact but the bronchus of the lower lobe is narrowed is appreciably attenuated and is cut rather short. In addition the entire mediastinum is displaced slightly to the right This could be due to the pleural effusion however fluid itself would not cause the destruction of the arch tecture of the bronchi there is a mass of some kind surrounding the lower lobe bronchus and probably extending up to include the main stem bronchus as well. There is no calcification or other characteristic to further identify the mass.

The last film (Fig 4) was made on October 21 n ne days before death and shows that there is an increase in the left pleural effusion. To summarize I would say then that there is marked left pleural effusion and a left pulmonary mass involving at least the lower lobe sufficiently to disrupt the architecture of the lower lobe bronchus, and probably involving the region of the left hilus as well causing altered architecture of the left main stem bronchus. The only other x-ray examination that the patient had was an intravenous urogram series which was normal

DR. PICK* Three electrocardiograms were obtained on this patient during his hospitalization. The first was taken on admission (September 30) and the last two days before his death (October 21) and are illustrated n Figs. 5 and 6 A record taken on October 5 was essentially unaltered when compared with the first.

The tracing taken on September 30 is abnormal with regard to rhythm and

*Dr. Alfred Pick, Associate Director, Cardiovascular Institute.



Fig. 2B Chest ray film taken in left lateral decubitus position on Sept. 30, 1966.



Fig. 1 Tomographic sections show deformity of the left main bronchus, narrowing of the bronchus to the left upper lobe and complete occlusion of the lower lobe bronchus.

contour There are regular P waves at a rate of 77, large and diphasic with a narrow and predominantly upright component in V suggesting some kind of atrial, probably right sided pathology. The ventricular complexes are of supraventricular shape and occur in regular sequence at a rate of 60 except for single earlier ones (labelled by dots) which are always linked to a P wave at P-R intervals of 0.32 to 0.40 second. Thus, we are dealing with a sinus rhythm and incomplete A-V dissociation caused by an advanced A-V block. The ventricles are dominated mostly by an A-V junctional pacemaker but at times are captured by sinus impulses that fall outside the prolonged junctional refractory period. The QRS axis in the frontal plane is about +90°. In V_2 and V_3, abnormally large S waves are present. The S-T is slightly depressed in I and V while the T waves are small throughout all leads and partly inverted in I, V and V_6. All these contour alterations are nonspecific but a pattern of left ventricular hypertrophy to be modified by some other more diffuse process could be suspected.

In the record of October 21 (Fig. 6) the ventricular complexes maintain a constant relationship to P waves at a prolonged P-R interval of 0.42 second, thus, only a first degree A-V block is present on this day. The P waves show (Lead II) some variability in size and spacing indicating a wandering pacemaker probably within the confines of the sinus node. The size of the QRS complexes in the frontal plane is reduced and the axis has shifted to about +130°. In the precordial leads, the transition zone now reaches up to V_6. All this suggests a positional alteration with clockwise rotation of the heart. Its cause may be a different position of the patient, perhaps due to elevation of the backrest because of shortness of breath, but it would also fit very well the shift of the mediastinum to the right as demonstrated by Dr. Levin.

Attempting to explain the change of rhythm in conjunction with the contour alterations, several possibilities come to mind. The varying A-V block could be caused by digitalis, but this is unlikely in the absence of typical S-T-T deformations, and with continued medication one would expect the A-V conduction disorder to persist or to progress, rather than to improve. Ischemic heart disease may be present but again the nonspecific character of the contour alterations renders this less likely. Any other diffuse and progressive process involving the myocardium



Fig 4 Chest x-ray film taken on Oct 1 1966

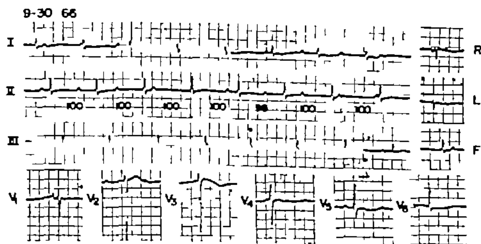


Fig 5 Electrocardiogram taken on Sept 30 1966. The numbers in Lead II are R R intervals sec 100.

may be responsible In tak ng nto accou t all the clinical data, n asion of the ven tricles, the atria and the proximal part of the specific conduction system by a malignant process an be considered

DR ILHER Dr Levin has raised two specters wl ich I should comment upon One he indicated tl at the configuration from a rad'ological point of view s consist ent with aortic valve d sease From the character of the pulse blood pressure and murmur only aortic stenosis is possible. This possibility can be dismissed because we know the heart in aortic stenosis dilates only when hypertrophy per se is an n sufficient compensatory mechanism At that point the ECG would show a very obvious left entricular hypertrophy pat

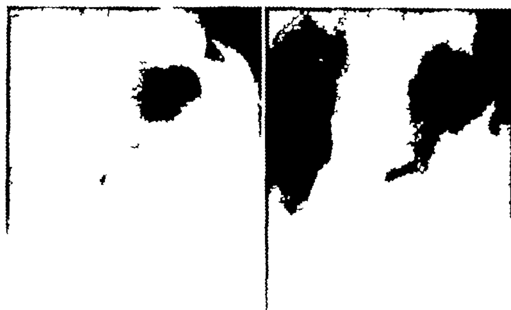


Fig 1 Tomograph sections show deformation of the left main bronchus, narrowing of the bronchus to the left upper lobe, and complete occlusion of the lower lobe bronchus

contour There are regular P waves at a rate of, large and diphasic with a narrow and predominantly upright component in V, suggesting some kind of atrial, probably right sided pathology. The ventricular complexes are of supraventricular shape and occur in regular sequence at a rate of 60 except for single earlier ones (labelled by dots) which are always linked to a P wave at P R intervals of 0.32 to 0.40 second. Thus, we are dealing with a sinus rhythm and incomplete A V dissociation caused by an advanced A V block. The ventricles are dominated mostly by an A V junctional pacemaker but at times are captured by sinus impulses that fall outside the prolonged junctional refractory period. The QRS axis in the frontal plane is about +90°. In V and V₄ abnormally large S waves are present. The S-T is slightly depressed in I and V₄ while the T waves are small throughout all leads and partly inverted in I, V₄ and V₆. All these contour alterations are nonspecific, but a pattern of left ventricular hypertrophy to be modified by some other more diffuse process could be suspected

In the record of October 21 (Fig 6) the ventricular complexes maintain a constant relationship to P waves at a prolonged P R interval of 0.42 second, thus, only a first degree A V block is present on this day. The P waves show (Lead II) some variability in size and spacing indicating a wandering pacemaker probably within the confines of the sinus node. The size of the QRS complexes in the frontal plane is reduced and the axis has shifted to about +130°. In the precordial leads the transition zone now reaches up to V₄. All this suggests a positional alteration with clockwise rotation of the heart. Its cause may be a different position of the patient, perhaps due to elevation of the backrest because of shortness of breath, but it would also fit very well the shift of the mediastinum to the right as demonstrated by Dr Levin

Attempting to explain the change of rhythm in conjunction with the contour alterations, several possibilities come to mind. The varying A V block could be caused by digitalis, but this is unlikely in the absence of typical ST T deformations, and with continued medication one would expect the A V conduction disorder to persist or to progress, rather than to improve. Ischemic heart disease may be present, but again the nonspecific character of the contour alterations renders this less likely. Any other diffuse and progressive process involving the myocardium



Fig 4 Chest -ra film taken on Oct 21 1966

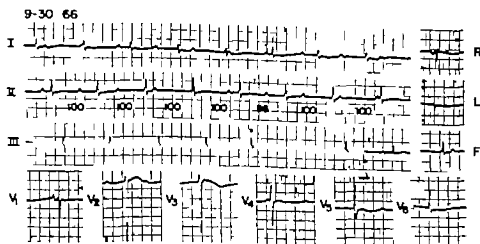


Fig 5 Electrocardiogram taken on Sept 30 1966. The numbers in Lead II are R R intervals sec /100

may be responsibl In taking into account all the cl nical data inv sion of the ventricles, the atria and the proximal part of the specific conduction system by a malignant process c n be considered

DR. SILBER Dr Lev has raised two specters which I should comment upon. One he indicated that the configuration from a radiologi l t f newt consi t ent with aortic alve disease From the haracter of the pulse blood pressure and murmu only aortic stenosis is possible. Thus possibil ty can be dismissed because w know th heart in ortic tenosis d'lates only when hypertrophy per se is an in sufficient compensatory mech nism. At that point the ECG would show a very obvious left ventricular hypertroph

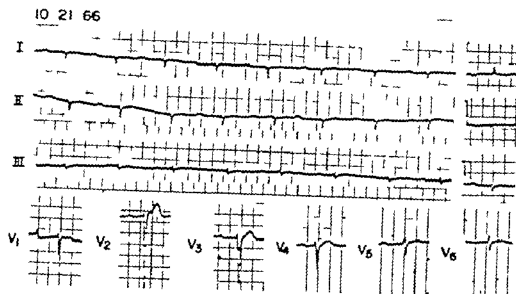


Fig. 6. Electrocardiogram taken on Oct. 21, 1966.

tern which it does not show in this patient. The other point that Dr. Levin raises makes me less secure. That is, he sees a mass. While there may be a mass, I will stick to the point of view that it is unrelated to the patient's congestive heart failure. If Dr. Pietra confronts us with a tumor, I feel it will not be responsible for this patient's heart failure. As Dr. Pick pointed out, there is nothing pathognomonic in the cardiac arrhythmia. Certainly it does not particularly speak for tumor in addition to my way of thinking. Most metastatic tumors involve the pericardium, and since the sinus node lies just below the pericardium, it is not infrequently involved by pericardial diseases. The A-V node, on the other hand, is remote from the pericardium, and pericardial involvement by tumor or inflammation does not produce disturbances of A-V nodal conduction. The latter is a nonspecific finding and, in the literature on primary myocardial disease, involvement of the conduction system of the heart by periarteritis, sarcoid, lupus, and so on is common. As Dr. Pick pointed out, this could simply be a digitalis effect or an effect of failure itself. I am left with the conclusion, therefore, that this man had a primary myocardial disease and his intractability was due to a complication which is very common in persistent heart failure of any form and origin, namely, recurrent pulmonary thromboembolism, which is a common complication and one still diagnosed too infrequently ante mortem. Heart failure per se is not a common cause of death in patients because the the heart rarely fails totally as a pump. In this case there is no evidence of systemic emboli, but it is likely there was a constant "seeding" of emboli into the lungs from the veins of the legs and the pelvic circulation itself, leading to progressive pulmonary hypertension, pulmonary insufficiency, and the death of the patient. I will leave to the Department of Pathology the classification of the causes of primary myocardial disease. Let me merely say that most of them are idiopathic; in other words, we do not demonstrate a cause. It is my feeling this will prove to be the case here, but I will not be surprised if confronted with some exotic granulomatous type of lesion or a myocardiopathy secondary to an arteritis. In conclusion, it is my impression that this patient had a primary myocardial disease, call it chronic myocarditis if you wish, and that death was due to a common complication, namely, recurrent chronic pulmonary thromboembolism.

DR. GOLDEN (Moderator).* The floor is now open for clinical discussion.

DR. BRAMS.** I would like to start with

*Dr. Jacob E. Golden, Senior Attending Physician, Department of Medicine.

**Dr. William A. Brams, Senior Attending Physician, Department of Medicine.

the question what was the occupation of this patient? Would he have anything to do with asbestos, because if he did one would have to think of a mesothelioma of the pleura which would account for the bloody sputum and pleuritic symptoms.

DR PIETRA He was working in a steel mill

DR. BRAMS At any rate there was a sudden onset here of pain in the right side of the chest cough and bronchopneumonia and the question is, was it really bronchopneumonia? Perhaps it was a pulmonary embolus. Then the pain shifted from the right side to the left side and that is a bit unusual too It was aggravated by respiration with stabbing indicating pleural involvement. But in spite of the massive effusion which would add weight to the patient he lost 20 pounds, which is suggestive of malignancy or tuberculosis or something of that sort but certainly malignancy has to be considered here. In addition a pleural rub was felt actually over the chest. There was a parasternal heave just to the left of the sternum which usually means that the right ventricle is working too hard I think he did have pulmonary emboli and that the right heart was trying to overcome it The pulses below the femorals bilaterally were absent that is curious. Perhaps he had emboli down there too. The thoracentesis revealed 500 c.c. of bloody fluid bloody fluid has many causes but the most common are malignancy mesothelioma sometimes or tuberculosis. The bronchoscopy I think, was very revealing It showed that the left main-stem bronchus formed a sharp angle with the trachea and was narrowed about 2 cm from its origin and very important, it was fixed Fixation of a movable organ is very suggestive of a malignancy no matter where when or how The tomogram as you heard Dr Levin explain showed irregularity in the contour of the main stem bronchus and more or less deformity and obstruction. So I would say that on the basis of the available information this man has primarily a bronchogenic carcinoma, thrombophlebitis, and as a result of that multiple emboli in various places, in his lungs, and possibly in his legs with that, in addition I would lean a little bit toward Dr Pick's interpretation of the causes for the arrhythmia.

DR. GOLDEN How would you explain the absence of pulsation?

DR. BRAMS Emboli

DR. GOLDEN From where

DR. BRAMS From the heart

DR. GOLDEN Any further comment? Dr Levin

DR LEVIN Dr Brams makes mention of mesothelioma which often is associated with pleural calcifications.[3] We did not see any pleural calcifications. It does not rule it out but there is no support for it as yet

DR. GOLDEN Dr Pick

DR. PICK Pulmonary embolism shows characteristic changes in the ECG and these were absent in this case

DR. GOLDEN Dr Mamby

DR. MAMBY* I have the original x ray at the time of first hospitalization.

DR. GOLDEN Will you bring it down. This was your private patient? If you have any other information to add to the history we would appreciate it Dr Mamby

DR MAMBY We saw this patient intermittently from approximately May until his present admission. He was under the care of another physician and he was seen initially at another hospital whose films I went to obtain this morning He presented largely exertional dyspnea then later he complained of the pain in his left shoulder and started to have the pleural reaction.

DR. GOLDEN Thank you Dr Levin do you see anything in these additional x rays which would throw some light on the clinical condition?

DR. LEVIN From some of the earlier films of March 1966 it appears that the heart at that time was moderately enlarged and I would interpret these as showing some pulmonary congestion it is of interest that at that time the effusion which was present was apparently limited to the left I cannot be sure that there may not be right intrapulmonary effusion mimicking a normal hemidiaphragm. It is also of interest in retrospect that I can see the lower lobe bronchus for a longer stretch than one normally sees and here too it seems mini-

*Dr Giuseppe G. Pietra Assistant Attending Physician, Department of Pathology

*Dr Audley R. Mamby Assistant Attending Physician, Department of Medicine.

mall deformed If the radiologist did not detect it then I do not blame him because I now have the benefit of seeing films made much later when the deformity is far more advanced

DR GOLDEN Dr Radner would you comment on the problem of fixation of the bronchial tree in the presence of neoplasm and in the presence of a bronchial effusion?

DR RADNER As Dr Brams said the fixation of the tracheobronchial tree and widening of the carina were always felt to be secondary to malignancy This is no longer held true because there are many other nonmalignant granulomatous processes that arise subcarinally in the left hilum that are capable of doing the same thing There is one exception and that is the encroachment of the bronchial lumen that Dr Levin demonstrated When we see that we are more inclined to consider malignancy Normally the tracheobronchial lumen may be shifted but not encroached on by benign masses When the wall itself is involved we think in terms of malignant processes.

DR GOLDEN What about the presence of the large pleural effusion?

DR RADNER Well the presence of the large pleural effusion which was presumably there right from the start was never explained either by cytology or pleural biopsy The fact that it was bloody is of little help. I do not think a blood effusion of this nature or size has any specific connotation at all Certainly you cannot rule out repeated pulmonary emboli with this kind of effusion but I would think in terms of some hilar mass pushing that left main stem bronchus up and encroaching on the lumen either as an extension of cardiac disease or involving the heart as well

DR GOLDEN Thank you Are there any further comments regarding the clinical course of this patient? Does anybody wish to express a different diagnosis than has been presented here by Dr Silber and Dr Levin?

Discussion

DR. PIETRA The postmortem examination revealed an extremely enlarged pericardial sac which compressed the lower lobe of the left lung (Fig 7) The surface of the pericardium was smooth and glistening except for a few white-yellow soft nodules on the left lateral surface (Fig 8) A large yellow white focally necrotic and hemorrhagic tumor mass filled the pericardial sac. The tumor seemed to arise from the epicardium invaded the parietal pericardium and the coronary sinus, protruding slightly through the coronary sinus ostium into the right atrium and extensively infiltrated the interatrial septum encroaching upon the A V node region preventing the identification of the A V node The tumor extended to the proximity of the bundle of His and this probably accounted for the A V block (Fig 9) Both atria and ventricles, however were free of tumor (Fig 10) Histologically the tumor was mostly composed of spindle-shaped cells with scanty cytoplasm and one regular mitotic figure per 3 to 4 high power fields (Fig 11,A) The tumor cells formed abundant reticulum and collagen but in some areas there was a looser cellular arrangement and less collagen In other fields the tumor cells had epithelial features and were arranged in papillary structures supported by delicate connective tissue septa (Fig 11,B) in the manner characteristic of mesothelioma.

Mesotheliomas are known to vary in appearance Cuboidal mesothelial cells in pseudoglandular or papillary arrangement may alternate with spindle-shaped cells similar to fibrosarcomatous elements. This property is shown also in tissue culture where mesothelial cells may grow either as collagen-producing spindle-shaped cells or as large epithelium like cells.[3]

The tumor surrounded the large vessels along the attachment of the pericardium invaded small veins, and metastasized to lungs and pleura. The metastases were few and small but accounted for the atypical cells seen on cytologic examination of the pleural fluid The necrotic tumor tissue obtained at needle biopsy of the pleura was possibly due to one of the pleural metastases or more likely to the fact that the needle reached the pericardial mass. Tumor cells were found in vascular spaces around vessels and bronchi suggesting a lymphogenous spread The left lung was

Dr Da M R Radner Director Division of Thoracic Medicine Department of Medicine

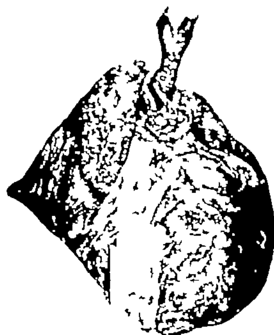


Fig 7 Frontal view of the chest organs The pericardial sac is enormously distended forming globular bulging mass.

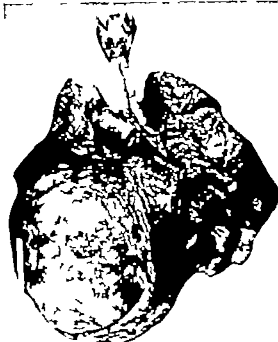


Fig 8 Posterior iew of the chest organs The descending aorta has been resected just below the bifurcation of the trachea. The esophagus has been removed The bulging pericardial sac is clearly visible On the lateral aspect near the ruler tumor nodule is seen The visceral pleura is thin and reveals no gross evidence of metastases. The hilar lymph nodes not clearly visible the picture ere ot enlarged.



Fig 9 Section of the eratrial nd interventricular septum The interatrial septum infiltrated by the tumor hich extends in proximit t the bundle of His (arrow). The A V node could not be identified. The right trium and en ricle are on the right side of the illustration. (Masson trichrome X8.)



Fig 10 The opened heart reveals part of the left atrium left entricle, and part of the scending aorta. The epicardium is covered by thick layer of soft, partially hemorrhagic tumor

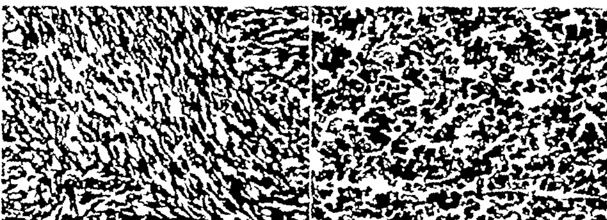


Fig 11 A The tumor is composed of bundles of elongated fibroblast like hyperchromatic cells with scant cytoplasm (Hematoxylin and Eosin ×485) B A different area of the tumor reveals cuboidal cells in papillary arrangement supported by delicate connective tissue septa containing thin walled blood vessels. (Hematoxylin and Eosin ×485)

collapsed partly because of compression by the tumor and partly because of pleural effusion Blood tinged fluid was found 600 ml in the left pleural space and 100 ml in the right The right lung showed in the lateral anterior aspect of the lower lobe large recent infarct A second infarct was present in the anterior aspect of the same lobe These were due to recent thromboembolic occlusion of the secondary branches of the pulmonary artery to the lower lobe Small emboli in various stages of organization were found in the tertiary branches of the pulmonary artery bilaterally and may account for the changing chest pain The sources of emboli were the left jugular and innominate veins, which were completely occluded by a recent thrombus and the prostatic plexus. The liver revealed marked central lobular congestion and necrosis. The kidneys were congested and showed enlarged glomeruli as seen in long standing right heart failure emphysema or cyanotic heart diseases. No changes of note were seen in other tissues.

Primary malignant mesotheliomas of the pericardium are rare Dr Jao, from our Department has found 26 cases in the English language literature. Daw and coworkers in their review accepted only 25 cases from the world literature and excluded many previous reports because of inability to review the original descriptions, among these the first one described in 1875 by Marchiafava[4] Mairot in his more complete thesis collected 68 cases from the entire world literature Of these only 11 were diagnosed during life by cytology or biopsy In most instances the symptoms were arthritic pain or chest pain cyanosis, dyspnea and intractable congestive heart failure In some cases, there was A V block due to extension of the tumor into the interatrial septum as in the present case [? ? ?] Incidentally instances of A V block due to metastatic tumor involving the interatrial septum have been also reported[1] In one instance the pericardial tumor manifested itself with pulmonary stenosis due to encroachment on the pulmonary outflow tract

DR. BRAMS What was the cause of the absent pulses in the legs?

DR. PIETRA This remains undetermined however there was no evidence of gangrene in the toes or feet at autopsy suggesting an embolic occlusion

DR REISS* I would like to ask Dr Silber how he can explain the absence of tamponade with the tumor completely encircling the heart it should have given little opportunity to expand

DR SILBER Did the tumor completely surround the entire heart?

DR. PIETRA Yes, it encased the heart like an armor forming a large mass which weighed 3 650 kilograms. This caused impaired diastolic filling of the heart a con

*Dr Eric Reiss, Chairman, Department of Medicine.

dition called in the literature tissue tamponade.[?]

DR. SILBER The description in the protocol of a heart that is dynamically pulsating both with a right ventricular lift and an apical impulse that is described as heaving is quite inconsistent with concretio cordis, where the heart is usually very quiet. Concretio cordis can certainly account for the passive congestion but I am certainly unable to reconcile the clinical findings with what was found at autopsy. I must accept that this is not true congestive heart failure but rather we are dealing with a restrictive effect upon the heart.

The one other thing I must ask is how you have decided that this is a primary mesothelioma of the pericardium? How do you know which came first pleural or the pericardial involvement? Primary mesothelioma of the pericardium is even more rare. If I am not mistaken the diagnosis requires the demonstration that there is absolutely no primary elsewhere in the body before a primary mesothelioma is accepted as such. When you have pleural involvement how do you distinguish between an origin in the pleura and metastases to the pericardium with encasement of the heart or primary involvement of the pericardium with metastases to the pleura?

DR. PIETRA Primary mesotheliomas of the pleura, which are the most common, and ordinarily associated with asbestosis,[12] usually involve diffusely the pleura and then secondarily extend to the pericardium. In this case we found a massive tumor which involved the pericardium and only a few small nodules in the pleura and lungs. In addition to the characteristic histologic picture, there was no evidence of any other occult primary tumor elsewhere.

DR. LEVIN Dr Pietra I do not understand as yet what caused the x ray appearance of the left main bronchus and lower lobe bronchus. Did the tumor encompass that area. I would expect that there would be pulmonary tumor surrounding that area. Now you said there were lung metastases, but I don t know whether they were large enough to produce the narrowing we see.

DR. PIETRA The tumor (as seen in Figs. 8 and 9) extended to the hilar region and around the left stem bronchus. Metastases were found microscopically in the lungs around the pulmonary arteries and veins. We have no sections from that particular area of the bronchus shown in the tomograms and we do not know whether the tumor involved the bronchial mucosa at that point.

DR. PIRANI* I would like to ask Dr Silber or Dr Pietra whether one might not expect a difference in functional behavior of the heart depending on the type of tumor surrounding the heart. In this case as I recall the tumor was rather soft because of either its nature or necrosis. In other types of tumors such as bronchogenic carcinoma or Hodgkin s disease, which are more common in this location we are confronted with firmer harder masses encasing the heart and I wonder if it makes any difference in terms of function especially when massive pericardial involvement is present.

DR. SILBER The literature on tumors of the heart as you know is not really very large and one can review it thoroughly with little effort. I once carried out a 50-year review of this literature but found no attention directed to this aspect that is, the firm or soft character of the tumor itself.

DR. BRAMS Was there any space between the visceral and parietal layers of the pericardium?

DR. PIETRA No it was filled with tumor.

DR. GOLDEN I wonder if Dr Pirani s question concerns also the time element involved because we know that chronic pericardial effusion can be accommodated to for quite a long time. If this tumor was a slow growing then the heart could have adjusted itself and explain the fact that there were easily detectable pulsations and it did not produce the concretio.

Anatomical diagnosis

Malignant mesothelioma of the pericardium with extension into the coronary sinus and to the A V conduction system and metastasis to lungs and pleura

Blood tinged pleural effusions (600 ml left 100 ml right)

Atelectasis of left lung

*Dr Conrad L. Pirani, Chairman, Department of Pathology

Infarcts ( ) of right lower lobe of the lung recent
Pulmonary thromboemboli recent and organizing
Thrombosis of left innominate and jugular veins and periprostatic plexus
Edema of left arm and legs
Passive congestion of lungs, liver spleen kidneys intestine chronic and acute severe
Emaciation moderate

REFERENCES

1. Friedberg C. K.: Diseases of the heart, ed. 2, Philadelphia, 1956, W. B. Saunders Company.
2. Selikoff I. J.: Occurrence of pleural calcification among asbestos insulation workers, Ann. New York Acad. Sc. 132(Art. 1):351, 1965.
3. Stout A. P., and Murray, M. R.: Localized pleural mesothelioma, investigation of its characteristics and histogenesis by the method of tissue culture, Arch. Path. 34:951, 1942.
4. Dawe, C. J., Wood, D. A., and Mitchell, S.: Diffuse fibrous mesothelioma of the pericardium, Cancer 6:794, 1953.
5. Marchiafava, E.: Un caso di endotelioma primitivo dei linfatici del pericardio, Atti Accad. Med. Roma 1:103, 1875-76.
6. Chaves, I.: Primary malignant mesothelioma of the pericardium, Dis. Chest 47:663, 1965.
7. Lopez-Cardoso, E., and Saltet, J. F.: A case of mesothelioma pericardii, Acta med. Scandinav. 178:301, 1965.
8. Mahaim, J.: Les tumeurs et les polypes du coeur, in Roth, F., et al, editor: Etude anatomo-clinique, Lausanne, Paris, 1945, Masson & Cie.
9. Malrot, A.: Contribution à l'étude des tumeurs primitives du péricarde. Thèse presentée à la faculté mixte de médecine et de pharmacie de Lyon, 16 Dec. 1960, Mâcon, 1960.
10. Kaplan, B. M., Pick, A., and Pirani, C. L.: Clinical Pathological conference, Am. Heart J. 73:245, 1967.
11. Waldhausen, J. A., Lombardo, C. R., and Morrow, A. G.: Pulmonic stenosis due to compression of the pulmonary artery by an intrapericardial tumor, J. Thoracic Surg. 37:679, 1959.
12. Selikoff, I. J., Churg, J., and Hammond, E. C.: Relation between exposure to asbestos and mesothelioma, New England J. Med. 272:560, 1965.

Fundamentals of clinical cardiology

Hypertensive encephalopathy

Frank A. Finnerty, Jr., M.D.
Washington, D. C.

Most physicians are familiar with the syndrome of a sudden elevation of blood pressure preceded by a severe headache and followed by convulsions, coma, or a variety of transitory cerebral phenomena. The pediatrician faces the problem in patients with acute nephritis, the obstetrician with toxemia of pregnancy, and the internist with hypertensive vascular disease. The intelligent management of these critically ill patients during the acute hypertensive episode has always been a difficult problem.

Pathophysiology

Hypertensive encephalopathy is associated with an increase in arterial blood pressure, diminished cerebral blood flow, cerebral arteriolar constriction, and cerebral edema.

Increased arterial blood pressure. Whatever the underlying disease—glomerulonephritis, essential hypertension, or eclampsia, the constancy of association of hypertensive encephalopathy with increased blood pressure and the frequency of a sharp rise in arterial pressure preceding the attack suggest that the hypertension or the phenomena which are concerned in its production are causally related to the cerebral syndrome. In the great majority of cases, the elevation of blood pressure is extreme, but it is occasionally noted that eclampsia and convulsions complicating acute nephritis (particularly in children) occur with a normal blood pressure. When the charts of these patients are critically analyzed, however, it is noted that the arterial pressure is about 140/90 mm. Hg. Although this figure is the conventional upper limit of normal for people over 25 years of age, a diastolic pressure of 90 mm. is certainly abnormal for most pregnant women and for all children. The average diastolic pressure in these particular groups is 60 to 70 mm. Hg. It is apparent, therefore, that a rise in diastolic pressure from 60 to 80 or from 70 to 90 mm. is very significant in the particular patient—as significant, indeed, as a rise in diastolic pressure from 90 to 110 mm.

Diminished cerebral blood flow. How then does this sudden hypertension cause the cerebral symptoms? Anatomic observations show that the hypertension does not produce the cerebral symptoms through the intermediacy of such gross lesions as cerebral hemorrhage or thrombosis. The usually sudden appearance and disappearance of the symptoms and the frequently bizarre neurologic picture (findings not to be explained by any one vascular lesion) immediately suggest that they may be due to focal or generalized cerebral ischemia.

A variety of experimental and clinical evidence testifies that symptoms equivalent to hypertensive encephalopathy can be produced by diminution in cerebral blood flow. Epileptiform convulsions have been

From the Department of Medicine, Georgetown University School of Medicine and the Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

produced in rabbits by ligating the arteries to the head and in man by temporarily compressing the carotid arteries. Cerebral ischemia must likewise be the cause of the epileptiform convulsions and coma that are the most striking features of the Stokes-Adams syndrome and a decrease in cardiac output with a resultant decrease in the amount of blood going to the brain must be the cause of the cerebral symptoms in postural hypotension. Coma and convulsions can be produced by postural hypotension.

It is plausible to say, therefore, that hypertension per se is not responsible for the encephalopathy since similar cerebral syndromes can be produced without any elevation of arterial pressure. The common denominator for hypertensive encephalopathy and postural hypotension—the sine qua non of all the above conditions—is a decreased cerebral blood flow due to cerebral vasoconstriction.

Cerebral arteriolar constriction. Practically all available evidence indicates that the elevated arterial pressure in the conditions now being considered is the result of increased constriction of the peripheral arterioles. Hypertensive vascular disease is characterized by an increased cerebral vascular resistance. Indeed, the highest recorded values for cerebral vascular resistance are in malignant hypertension and in hypertensive encephalopathy. When the retinal arteries of an eclamptic patient are inspected, they are found to be very narrow. Immediately following effective hypotensive therapy, the arteries are seen to be full again. Indeed, blindness in acute hypertensive states has been shown by ophthalmoscopic examination to be accompanied by complete spastic obliteration of the retinal arteries, which later become patent, with restoration of vision as the hypertension subsides.

The sudden coming and going, the variability, and the transitory nature of the cerebral phenomena that are seen in all types of hypertensive encephalopathy seem to be explained best by postulating that there is a sudden decrease in cerebral blood flow due to a sudden increase in cerebral vasoconstriction. The cause of the cerebral vasoconstriction is not clear. The cause of the generalized vasoconstriction characterizing all types of hypertension remains an enigma.

Cerebral edema. That cerebral edema is present in some cases of hypertensive encephalopathy cannot be denied. Evidence for cerebral edema is found clinically in spinal fluid pressure measurements exceeding 400 mm. of water and at the autopsy table in a 20 to 30 per cent increase in brain weight, flattening of cerebral convolutions, and reduction in the size of the ventricles. Although the cause for the cerebral edema also is unknown, the most likely hypothesis seems to be that set forth by Fishberg. He stated that when the arterial pressure rises before the attack (due to peripheral vasoconstriction), the constriction of the cerebral arterioles is not as powerful as that of the arterioles elsewhere in the body. Consequently, there is a rise in pressure in the intracranial capillaries, acceleration of filtration, and the formation of edema. It is interesting that the incidence of hypertensive encephalopathy, particularly eclampsia and encephalopathy following chronic hypertensive disease, has greatly decreased during the past ten years. The most plausible explanation seems to be the almost routine use of thiazide diuretics in the treatment of the pregnant patient and in the antihypertensive armamentarium.

Differential diagnosis

Two syndromes must be differentiated from true hypertensive encephalopathy: (1) acute anxiety state with labile hypertension and (2) acute pulmonary edema due to hypertensive heart disease. Despite extremely high levels of arterial pressure in both these disease states, the use of hypotensive agents is usually not indicated. In the patient with anxiety, there is frequently a history of multiple complaints including tension headaches and dizziness. Observation of the patient reveals sighing respirations, and physical examination shows normal retinal arteries and no cardiomegaly. The laboratory reports a normal urinalysis and electrocardiogram. Since the site of the major abnormality in these patients seems to be supratentorial, intelligent therapy should be directed toward the relief of anxiety. In these patients, pentobarbital sodium, amytal sodium, or

chlordiazepoxide hydrochloride administered intravenously will frequently be followed by prompt alleviation of the symptoms and then by a remarkable fall in arterial pressure.

Although the patient with pulmonary edema due to hypertensive heart disease may present with extremely high levels of arterial pressure, correction of the pulmonary edema usually results in a drastic reduction in blood pressure. Thus, when obvious signs of acute pulmonary edema (gallop rhythm, pulsus alternans, etc.) are present in a patient whose arterial pressure is excessively elevated, morphine, digitalis, and diuretics are the drugs of choice rather than strictly antihypertensive agents.

Since encephalopathy is always accompanied by an increased vascular resistance—best reflected clinically by a high diastolic pressure—and since clinical experience has shown that clearing of the sensorium, cessation of convulsions, and release of vasoconstriction follow reduction in blood pressure, the primary aim of therapy should be reduction of arterial pressure.

Treatment of hypertensive encephalopathy. From the practical standpoint, the drug chosen to reduce the arterial pressure depends on the clinical condition of the patient, particularly on the degree of cerebral ischemia present. If the condition of the patient is such that a $1\frac{1}{2}$ to 2 hour delay in reducing the arterial pressure would not be harmful, parenteral reserpine is the drug of choice. On the other hand, if immediate reduction in arterial pressure is necessary, e.g., if the patient is convulsing or on the verge of a convulsion, diazoxide becomes the drug of choice.

RESERPINE. Parenteral reserpine has now been available for more than ten years and has become recognized as the most useful agent for the management of acute hypertension. The average effective intramuscular dose is 5 mg. There is no advantage in administering the drug intravenously. Although increasing the dosage of reserpine from 5 to 10 mg. slightly increases the hypotensive effect, it greatly increases the toxicity. Following intramuscular injection, there is a delay in onset of action of at least $1\frac{1}{2}$ hours; the maximal hypotensive effect is not noted for 3 to 4 hours. The average duration of action is $7\frac{1}{2}$ to 8 hours. At the time of the maximal hypotensive effect there is a 20 to 25 per cent average reduction in mean arterial pressure. A slight reduction in the heart rate usually occurs.

Just as important as the fall in arterial pressure following parenteral reserpine is the calming effect of the drug. This effect becomes apparent 45 minutes following injection, reaches its height at the time of the maximal hypotensive response, and lasts 11 to 12 hours. Excitable, tense patients commonly are found in a normal sleep; if not spoken to or disturbed, they remain in this state until the effect of the medication has worn off.

Combination With Other Drugs. Similar to oral reserpine, parenteral reserpine enhances the hypotensive effect and prolongs the duration of action of other antihypertensive and diuretic agents. Since the advent of diazoxide, combinations of reserpine and veratrum or reserpine plus hydralazine are no longer used in our hospital in the management of acute hypertension. In patients with encephalopathy due to toxemia of pregnancy or glomerulonephritis, where sodium retention plays a more important role, 40 to 60 mg. of furosemide are now combined with reserpine. In addition to a prompt sodium diuresis, this combination results in a 25 to 30 per cent reduction in mean arterial pressure which frequently lasts for 10 to 12 hours.

Limitations Of Reserpine. Although a very useful agent, parenteral reserpine has many limitations.

1. Since there is a delay in onset of action of $1\frac{1}{2}$ to 2 hours, reserpine cannot be relied on as the sole therapy in patients who show signs of severe cerebral ischemia.

2. It can be used only for short term therapy. After 48 hours, nasal congestion, flushing of the face, and lethargy become objectionable to the patient.

3. Nasal congestion and increased tracheobronchial secretion occasionally occur in infants delivered to mothers treated with the drug. Alerting the nursery personnel of this possibility, so that the infants are kept on their side and prompt correction of nasal congestion will prevent serious fetal complications.

4 Occasionally signs of Parkinsonism have been noted when reserpine has been continued over 72 hours.

5 Since reserpine frequently potentiates the sedative and occasionally the hypotensive action of the barbiturates, these two drugs should not be administered concomitantly.

6 Local and particularly general anesthesia may occasionally potentiate the hypotensive effect of reserpine causing profound falls in arterial pressure. Knowledge of this possible potentiation and the prompt administration of norepinephrine or phenylephrine usually restores the arterial pressure promptly.

Despite all these limitations parenteral reserpine remains the most useful agent in the treatment of encephalopathy when a delay in action of two hours would not be harmful to the patient.

DIAZOXIDE. During the past several years we have had experience with an agent that chemically resembles chlorothiazide but pharmacologically is quite different. When administered by mouth diazoxide reduces arterial pressure only slightly and causes sodium retention and hyperglycemia. When administered intravenously however it is a very potent vasodilating agent. The average effective dose is 300 mg. given rapidly undiluted.

Experience has shown that the speed of injection is important in determining both the magnitude of the blood pressure fall and the duration of hypotensive effect. When less than 300 mg. of diazoxide is administered or when 300 mg. is not administered in a 10 to 15 second period only a short hypotensive response is noted. In a few hypertensive patients who weigh over 150 pounds, 300 mg. of diazoxide may produce only a slight reduction in arterial pressure for a short duration, e.g., a duration of 30 to 60 minutes instead of 8 to 9 hours. If a satisfactory fall in arterial pressure does not follow 300 mg. of diazoxide the dosage should be increased to 5 mg. per kilogram.

To date 314 patients with various types of hypertensive encephalopathy have been treated with diazoxide. A 35 per cent average reduction in mean arterial pressure occurs during the first two minutes. During the next three to five minutes the arterial pressure increases gradually leveling off at an average 20 per cent below control levels. No signs of postural hypotension, cerebral ischemia, or collapse are noted. The average duration of action is 9 to 11 hours. An excellent response (more than a 25 per cent fall in mean arterial pressure with complete clearing of the neurologic state and absence of side effects) has occurred in 242 patients (77 per cent).

The fall in arterial pressure with diazoxide was consistently associated with an increase in cardiac output (+40 per cent) and decrease in total peripheral resistance (−41 per cent). These hemodynamic changes persisted long after the peak action of the drug had been reached. The mechanism responsible for the reduction in total peripheral resistance is not clear from our studies, but animal data suggest that the reduction in peripheral resistance is a direct action on the arteriolar muscle. From the cardiac hemodynamic standpoint, diazoxide resembles hydralazine since both agents cause an increase in the cardiac output and heart rate. Determinations of actual cerebral blood flow have not been performed in this laboratory but the lack of signs of cerebral ischemia accompanying the reduction in arterial pressure and the increase in cardiac output strongly indicate that there is at least maintenance of the cerebral blood flow even at the point of the greatest magnitude of hypotensive action of diazoxide. It is significant also that the level of blood urea nitrogen does not increase following the intravenous administration of diazoxide.

Limitations Of Diazoxide. Although the immediate onset of action, maintenance of cardiac output, lack of significant side effects, and the fact that it can be administered repeatedly without the development of drug resistance make diazoxide an extremely valuable agent for the treatment of acute hypertension, it does have certain limitations.

1 Transitory hyperglycemia lasting no more than 12 hours regularly follows intravenous diazoxide. Recent reports of Wolff and associates[3] and studies in our laboratory[4] have demonstrated that pretreatment of patients with tolbutamide will effectively prevent the hyperglycemic effect of diazoxide. It would seem, therefore

that when diazoxide therapy is administered for more than a 48 hour period it should be combined with tolbutamide.

2. The alkaline nature of the medication makes any extravasation outside the vein painful. Although such extravasation is associated with a severe burning sensation which lasts one to two hours, no sloughing of tissues has occurred.

3. In 50 per cent of the pregnant patients who were in labor the fall in arterial pressure following diazoxide was associated with temporary cessation of labor. This probably represents part of a generalized relaxation of the smooth muscle and is not a toxic reaction of the drug. Awareness of this development and institution of oxytocics promptly restarted labor.

4. The fall in arterial pressure following diazoxide is consistently followed by a reduction in urinary sodium excretion. Because of the importance of sodium retention in the pathogenesis of both toxemia and glomerulonephritis a combination of chlorothiazide or acetazolamide was routinely added to diazoxide when treating these diseases. Recent studies in this laboratory have shown that the sodium retention which accompanies diazoxide can completely be prevented by pretreatment of the patient with 40 to 60 mg. of furosemide. Thus, when 300 mg. of diazoxide was administered 30 minutes following furosemide the 35 per cent decrease in mean arterial pressure was associated with a six-fold average increase in urinary sodium excretion. Of even more importance was the observation that the fall in arterial pressure was associated with a 34 per cent average increase in renal blood flow. If these preliminary findings are documented by a larger number of patients, it would seem that the combination of furosemide plus diazoxide would not only be the treatment of choice for patients with hypertensive encephalopathy but would also be the only safe treatment for hypertensive patients with impaired renal function. Studies are currently being carried out to determine the value of this combination in normotensive uremic patients.

Summary

The drug chosen to reduce the arterial pressure in patients with hypertensive encephalopathy depends on the degree of cerebral ischemia present.

If the clinical condition of the patient is such that a $1\frac{1}{2}$ to 2 hour delay in reducing the arterial pressure would not be harmful, parenteral reserpine is the drug of choice.

If immediate reduction in arterial pressure is necessary, intravenous diazoxide is the drug of choice. Preliminary studies suggest that the combination of furosemide plus diazoxide produces a greater fall in arterial pressure and increases both the renal blood flow and urinary sodium excretion.

REFERENCES

1. Wolff, F. W., Grant, A. M., and Wales, J. K.: Reversal of diazoxide effects by tolbutamide. Lancet 1: 1137, 1967.
2. Davidov, M., Kakaviatos, N., and Finnerty, F. A., Jr.: Unpublished data.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

Ethacrynic acid and furosemide

John H. Laragh, M.D.
New York, N. Y.

After extensive clinical trials in the past year the new diuretic agents, furosemide and ethacrynic acid, have both been made generally available. Because they are more powerful than all other diuretics, these two agents provide a new resource for treatment of unresponsive patients with heart failure, cirrhosis, and nephrosis, and for other states of fluid retention. Moreover, they have already constituted a new tool for elucidation of the renal transport mechanisms involved in sodium conservation. An appreciation of the pharmacological effects of these agents is essential for their safe and effective use.

General properties

The two new agents are quite dissimilar in chemical structure. Ethacrynic acid is an α-β-unsaturated ketone derivative of phenoxyacetic acid, while furosemide is a sulfonamide compound with an anthrone ring attached. As compared with conventional thiazide diuretics, both are stronger organic acids with pKs of about 3.8, and both are more water soluble. Since their actions are qualitatively very similar to thiazides, it is possible that their greater potency is related to these physicochemical differences, which might permit a broader distribution in the nephron.

Despite differences in chemical structure, ethacrynic acid and furosemide can be discussed together because their physiological effects for the most part are qualitatively very similar. Furosemide may differ slightly because it appears to be a weak inhibitor of carbonic anhydrase. Also furosemide, like thiazides, can produce hyperglycemia. This effect has not been observed with ethacrynic acid. Quantitatively, ethacrynic acid is more potent by weight, and it may have a slightly greater absolute potency. Furosemide exhibits an unusually broad dose response curve. When lower dosages are employed, it resembles other thiazide diuretics. Despite greater natriuretic potency, both ethacrynic acid and furosemide exhibit less antihypertensive activity than do conventional thiazides. This point is relevant to the still unresolved problem of the mechanism of antihypertensive action of thiazide diuretic agents.

The greater diuretic potency of these two new compounds in blocking renal tubular sodium reabsorption is a most impressive phenomenon. Thus, in one of our patients with advanced congestive heart failure, the intravenous administration of a single dose of ethacrynic acid caused an 18 pound weight loss in the subsequent 24 hours. Clearance data revealed that the drug had caused the excretion of as much as 32 per cent of filtered sodium, 47 per cent of the filtered chloride, and 46 per cent of filtered water. Under special con-

From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital in the City of New York.
This work was supported by Grants HE-01275 and HE-05741 from the National Institutes of Health.

ditions, others ha e observed even higher rejection fractions.

Mode of action

In considering the mechanisms of action of ethacrynic acid and furosemide it is helpful to compare their properties with those of the longer-known thiazide diu retics. The two new agents can be viewed as more powerful thiazide agents because in most respects their physiological effects grossly resemble those produced by thia zides Thus, the pattern of electrolyte excretion during d uresis with kaliuresis and a tendency towards disproportionately greater loss of chloride than sodium the additive effects when combined with or ganomercurial agents carbonic anhydrase inhibitors, or aldosterone antagonists, and the dual effects on uric acid clearance are all similar to what has been observed with thiazide agents. In addition ethacrynic acid and furosemide both interfere with urinary dilution (free water formation) also a property of thiazide diuretics.

While possessing all of the diuretic properties characteristic of thiazide agents, ethacrynic acid and furosemide exhibit add tional physiological effects which ma explain in part their significantly greater absolute potency Thus, unlike thiazides, ethacrynic acid and furosemide both inter fere with urinary concentrating capacity ($T^c_{H_2O}$) This suggests that the new drugs act to depress sodium reabsorption in the loop of Henle and in the ascending limb whereas thiazides may only act more distally in the more cortical placed distal tubular d luting segment Another differ ence from thiazides is the observation that on acute adm nistration the two new agents do not depress and may actually increase glomerular filtration and renal plasma flow In addit on n balance studies the two new drugs tend to produce greater and more sustained urinary hydrogen loss.

Indications

Because of their great potency thacrynic acid and furo emid are especially useful and even l f sav ng for desperately ll or unresponsive ede tous patient some of whom may exh bit electrolyte derangements and azotemia. The new drugs should always be given intermittently and in creased in step-wise fashion as responsive ness is determined In more difficult cases the new drugs can be effectively combined w th spirolactone carbonic anhydrase inhibitors, mercurial agents, or corticosteroids In most desperate situations, they may even be given during infusion of mann tol salt poor albumen or packed cells.

Because of their rapidity of action the intravenous use of these drugs can be especially rewarding in the treatment of emergent situations such as acute pul monary edema. Diuresis as great as 3 L. can be produced in a 4 hour period

The use of these new drugs in outpatients cannot yet be generally recommended and should be restricted to patients who are un responsive to conventional therapy who can be carefully supervised and preferably whose responsiveness to the new drugs has been established during hospital observation.

The control of untoward effects

Both for efficiency and safety we have long advocated an intermittent rather than a daily dosage regimen in the use of either thiazide or organomercurial agents. This dictum is even more applicable to the more powerful new agents. Using an intermittent schedule in which the drug is given for one to three consecutive days followed by a two to four day rest period time is allowed for responsiveness to the agent to be restored and for the natural correction of any induced electrolyte derangements

Dealing with electrolyte distortions produced by either ethacrynic acid or furose mide presents a problem somewhat s m lar to that observed with thiazides. It bas cally invol es the anticipation and control of chloride potassium and also h drogen ion depletion To cope with these problems, n add tion to interm ttent therapy t may at times be necessary to use a daily maintenance regimen employing one of the potassium-retaining nhibitors of endogenous aldosterone Supplements of potassium as the chloride salt may also be necessary This procedure is not always satisfactory because large amounts of

potassium chloride (KCl) can cause intestinal lesions and can disturb heart function. At times additional chloride and hydrogen repletion with ammonium or arginine salts may also be needed. Since excessive removal of bicarbonate-free extracellular fluid contributes to alkalosis in certain situations, a restorative infusion of sodium chloride may be required.

Most of these precautions in usage are required only because of the greater potency inherent in these two new compounds. Notwithstanding these precautions, it is already apparent that the two new agents are very significant contributions to therapeutics. They have also proved to be useful and exciting tools for renal physiologists.

REFERENCES

1. Cannon, P. J., Heinemann, H. O., Stason, W. B., and Laragh, J. H.: Ethacrynic acid. Effectiveness and mode of diuretic action in man, Circulation 31:5, 1965.
2. Stason, W. B., Cannon, P. J., Heinemann, H. O., and Laragh, J. H.: Furosemide. A clinical evaluation of its diuretic action. Circulation 34:910, 1966.
3. Laragh, J. H.: The proper use of newer diuretics, Ann. Int. Med. 67:606, 1967.

Annotations

The intrathoracic extracardiac pneumatic ventricular assistor

With the development of open heart surgery and the impact of increased knowledge of heart disease careful attention has been directed toward mechanical devices to assist the failing heart. Many mechanical devices have been developed employing varieties of principles, all of which are directed to supporting the circulation and relieving the work of the heart. Ideally these devices should be easily and quickly installed with minimum surgical trauma, be simple to operate, be capable of maintaining adequate cardiac output with normal pulsatile flow and, preferably, function without heparinization of the patient.

In 1966, Anstadt and associates described a positive and negative phase pneumatic extracardiac ventricular assistor which could be placed on the ventricles within a matter of minutes and could maintain normal ventricular output with pulsatile flow without heparinization. In 1957 Vineberg[4] had designed a similar apparatus but with only a positive phase.

The Anstadt apparatus is simple in construction and operation consisting of an assistor cup enclosed in a glass housing with a plastic diaphragm, and is operated with a positive air pressure of 120 to 140 mm. Hg and a vacuum pressure of −120 mm. Hg. The rate is controlled by an alternator. The assistor cup can be applied easily and rapidly through either lateral thoracotomy or sternal splitting incision. It is held on the heart by a separate sustained negative system of a vacuum of −80 mm. Hg.

Anstadt and associates[2] have demonstrated that application of the ventricular assistor after induced ventricular fibrillation will support dogs for 16 hours with normal physiological function after defibrillation. Skinner and associates have demonstrated that acute occlusion of the circumflex branch of the left coronary artery produces death in 75 per cent of dogs without ventricular assistance and that 65 per cent of the animals survive with assistance. In our laboratory anterior descending coronary artery ligation in the pig produces ventricular fibrillation and death in 100 per cent of the animals in 2 to 25 minutes. We have demonstrated that ventricular assistance will allow the heart to be defibrillated and sustain output.

There are at least three limited clinical areas that would bear thought and investigation in relation to its usage. A limited number of selected patients suffering from acute coronary occlusion with shock or fibrillation might well re-establish enough blood supply to the myocardium after ventricular assistance, when all other means of resuscitation have failed, to allow survival as demonstrated in the pig. This is hypothesized on the basis that with the maintenance of adequate ventricular output and perfusion pressure, sufficient collaterals are re-established to the myocardium following acute coronary occlusion.

There are a limited number of patients whose heart will not sustain adequate cardiac output after open-heart surgery. These patients cannot be maintained on cardiopulmonary bypass for long periods of time and consequently the ventricular assistor would be a valuable adjunct in these cases. Deheparinization could be performed and cardiopulmonary bypass terminated while maintaining adequate ventricular output and perfusion with the ventricular assistor. Perhaps the weakened myocardium could be assisted in this fashion until the heart has recovered sufficiently to maintain adequate output and perfusion. This would be especially important in cases of valvular repair with superimposed coronary artery disease.

Organ preservation using the present techniques of mechanical perfusion, hypothermia, and hyperbaric oxygen as well as other additive agents, has not been highly successful in maintaining normal organs. As Anstadt's ventricular assistor has the ability to support pulsatile circulation for 16 hours, it is obvious that the ventricular assistor could be used to sustain in vivo the heart or other organs while the recipient patient is being prepared for implantation.

In summary the potential of a simplified pneu

matically driven extracorporeal ventricular assistor is outlined. With further development and careful selection of patients, this device may make a valuable contribution to patients with heart disease.

Carl H. Almond, M.D.
Department of Surgery
University of Missouri Medical School
Eugene E. Elefson, D.V.M.
Richard E. Hoffer, D.V.M., M.S.
Department of Veterinary Medicine and Surgery
University of Missouri School of Veterinary Medicine
Columbia, Mo.

REFERENCES

1. Wugg, W. L., Webb, W. R., and Cook, W. A.: Assisted circulation, Ann Thoracic Surg 3:247, 1967.
2. Anstadt, G. L., Schiff, P., and Baue, A. E.: Prolonged circulatory support by direct mechanical ventricular assistance, Tr Am Soc Artif Int Organs 12:72, 1966.
3. Vineberg, A.: Mechanical heart massager, Canad. M. A. J. 77:195, 1957.
4. Skinner, D. B., Anstadt, G. L., and Camp, T. F. J.: Acute circulatory support by mechanical ventricular assistance following myocardial infarction. Presented to the American Association for Thoracic Surgery, New York City, April 19, 1967.

The cause of transplanted heart valve homograft persistence

Heart valve homografts have been successfully transplanted both in experiment and in the clinic. Apart from operational techniques, heart valve transplantation involves a basic problem which has so far failed to meet with a satisfactory answer, namely, the problem of what happens to the transplanted tissue. The transplanted materials are collagenous structures which are expected to be able to take over the valve function immediately after the operation and subsequently to keep on functioning reliably over a period of years. It is difficult to imagine that the transferred fragile homologous leaflets can stand the strain of functional wear over a continued period of time, considering that they are exposed to resistance from the recipient. One would rather expect them to suffer destruction either through immunologic reaction or through some unspecific inflammation. Amazingly, however, the transplanted aortic valve homografts have turned out to be of highly stable nature as can already be gathered from the earlier studies of Lam,[13] Murray,[14] or Beall and colleagues. Aortic valve leaflets floating freely in the blood stream could be observed to remain macroscopically unchanged for months and years after transplantation. This finding has been confirmed by the results achieved by Ross[17,18] and Barratt Boyles. Similar durability in regard to the mitral valve leaflets may be derived from the studies of Bernard and colleagues. What enables these comparatively fragile structures, which are transplanted in general not even alive but as dead tissue after undergoing a chemical sterilization process, to retain this extraordinary persistence?

The ultimate condition of the homograft tissue after transplantation is practically not affected by the transplantation immunology.[11,16] In what manner are the valve grafts preserved and revitalized? We have made the following pertinent experiments.

Single homologous aortic valve leaflets, in some cases obtained by sterile methods and in other instances sterilized in ethylene oxide and freeze-dried, were planted into the descending aorta of 26 dogs. As soon as the blood stream was released, the leaflets formed like a little cord pulling across the vessel lumen in response to the tension of aorta walls. The destiny of the leaflets was submitted to subsequent studies at various intervals up to 19 months. In a second series, corresponding leaflets were implanted subcutaneously into six dogs.

As a cord the leaflets were preserved in the blood-stream macroscopically unchanged. According to microscopic findings, the structures became necrotic in a slow process which proceeded without any inflammatory reaction or any supplementary effect from vessel-carrying granulation tissue; the leaflets became invaded by fibroblasts and revitalized within a period of 12 to 19 months (Fig. 1). They now consisted of cell-poor connective tissue with collagenous fibers that are oriented in the direction of tension of the aortic wall. The subcutaneously implanted homograft tissue in contrast became completely organized within 6 weeks and could no longer be recognized either macroscopically or microscopically. An unspecific inflammatory reaction only could be observed within this process.

Thus, according to these tests the same tissue shows a different behavior in different places of the organism. In one instance, it is slowly being revitalized; in the other it rapidly meets with destruction. The differing behavior of the same tissue in two different locations of the same organism calls for an explanation. We suppose that the specific position within the blood stream is of significance for the durability of the aortic valve tissue. Dead connective tissue, no matter whether of autologous or of homologous origin, causes inflammation in



Fig. 1 Cordlike aortic alve leaflet transplanted 6 months in dog Note the still recognizable necrotic areas (arrow), the immigrating fibrous cells, and the bsence of any inflammation (Hematoxylin and eosin ×40.)

most parts of warm-blooded organism, followed by dissolution of the dead tissue and its replacement by granulation tissue The impulse for these de elopments probably derives from diffusible substances emanating from the necrosis and appearing in concentration discernible to the recipient. It is in this way only that the existence of a necrosis is t all noticed Considering this mechanism an aortic valve homograft transplanted subcoronarily thus enjoys very unique special status. The transplanted valv homografts float in the bloodstream. Diffusible substances are onstantly being rinsed aw y and thus are unable to take impact. Hence, it does not even become known that dead tissue is located in this part. A y reaction aimed at destroying the necrosis, therefore, remains absent It is on the contrary imperceptibly revived I this context, it may be of interest that tw additional examples exist where alien alive (respectively dead) tissue can remain within the organism w thout evoking any defense reaction, and that in both these cases rinsing of tissue takes place.

Homologous cornea can be transplanted ith success rate of 70 per cent.[20] The transplanted cornea is alive and nevertheless fails to evoke immunologic reaction. There must be particular cir cumstances to prevent rejection. The cornea is being profusely rinsed, t the front by the stream of tears, at the back by the chamber fluid The latter is exchanged about 9 times within 24 hours.[14] By means of this rinsing, diffusible substances pt to reveal the presence of homologous cornea can be removed in exactly the same way as by the blood stream in the case of the aortic valv The front chamber of the eye, or the place w thin the cornea, respectively have been used for the study of homologous and heterologous cartilage transplantation by arious investigators because of its particular location which protects it against immunologic reactions.[24] I our opinion, rinsing by the chamber fluid is the prerequisite for such protection.

To cover defects of the dura, homologous, freeze-dried dura mater is transplanted On the occasion of secondary craniotomies one or two years later it has been observed[13,28] that the transplanted dura in its central section contained wide areas of entirely unchanged tissue, with newly formed tissue slowly invading the transplanted matter in the peripheral areas only There were no signs of any inflammation. The dura mater too is being rinsed. The liquor stream is slower than the chamber fluid, but it amount is larger (145 ml.) Seventy to 100 ml. are produced each day and resorbed in the sphere of the subarachnoidal area.[14] A liquor movement is caused by the pulsations of the brain.[12] Like the aortic valve, or the cornea, the dura mater is brady trophic, cell-poor tissue That means small amount of substance only may be assumed to arise and t diffuse into the liquor cerebrospinalis. In principle, all of the three examples show identical conditions. The "rinsing prevents the discovery of the tissue alien to the body

The second part of the problem involves the ultimate destiny of the transplanted valv homografts. It is hardly feasible that in the long run dead tissue can hold out against the functional burden of an aortic valve. Late failures of homologous aortic valve transplantation will fail to occur only if there exists possibility for revitalizing th transplanted structures. In the case of valv homografts transplanted orthotopically or into the descending aorta it is by no means simple to ascertain whether the collagenous fibers of these alve leaflets are being substituted by new ones. In our own tests according to the technique of Lam and associates,[18] we[6] have been unable to find any necrosis. So did Hudson [17] who failed to show necrotic areas in the leaflets of aortic valve homografts in human beings. The thin fragile leaflets are probably very soon refurnished ith cells, so that discernible necrosis never comes about. The cordlike leaflet, on the other hand is considerably thicker As a result of the fibrin coating and the fibrous capsule originating therefrom it develops into a solid cord in which the collagenous elements finally integrate into material that is homogenous to far-reaching ex tent Here, the necrosis and the revitalizing process are more distinctly recognizable.

W consider the above findings to be evidence of the fact that revitalization of implanted dead heart-valv homografts is possible. The heart valves of mammals are all constructed of the same connective tissue elements and, correspondingly not very active immunologically It may be assumed that the described rinsing effect protects heterografts in exactly the same w y as it protects homologous ones. I animal experiments Duran and Gunning[8] have observed heterologous aortic valve grafts for up to 8 months. Binet and associ ates were subsequently encouraged to implant aortic valves of pigs and calves in human beings too, and came to the conclusion that such heterologous grafts are definitely being tolerated

Hen H Hirsch D med. Prof f Chirurgie
Horst Henke Dr med.
Chirurgische U iversitätsklinik
Frankfurt a.M
B ndesrepublik Deutschland

REFERENCES

1. Barratt Boyes, B. G.: Homograft aortic valve replacement in aortic incompetence and stenosis, Thorax 19:131, 1964.
2. Barratt Boyes, B. G., Lowe, J. B., Cole, D. S., and Kelly, D. T.: Homograft valve replacement for aortic valve disease, Thorax 20:495, 1965.
3. Barratt Boyles, B. G.: A method for preparing and inserting a homograft aortic valve, Brit. J. Surg. 52:847, 1965.
4. Beall, A. C., Jr., Morris, G. C., J., Cooley, D. A., and De Bakey, M. E.: Homotransplantation of the aortic valve, J. Thoracic & Cardiovas. Surg. 12:497, 1961.
5. Bergh us, J. G., Rastelli, C., va Fleet, P. D., T tus, J. C., Swan, H. C. J., and Ellis, F. H.: Homotransplantation of the canine mitral h. Circulation 29:47, 1963.
6. Bernard, A., Senning, A., Gander, M., Schad, N., Stucky, L., and Pfenninger, E.: Funktionelle und morphologische Ergebnisse der experimentellen Homotransplantation der Mitralklappe. Thoraxchir. 11:94, 1966.
7. Bernard, A., Ringdal, R., Babotai, J., Linder, E., Kra enbuhl, H. P., and Senning, A.: Zur Homotransplantation der Mitralklappe. Tech ik postoperat ve Resultate. Thoraxchir. 13:89, 1965.
8. Bigelow, W. C., Yao, J. K., Aldridge, R. E., Heimbecker, R. O., and Murray, G. D.: Clinical homograft val t anspla t tion. J. Thoracic & Cardiovas. Surg. 48:333, 1964.
9. Binet, J. P., C rpentier, A., and Langlois, J.: Heterotransplant te der Aortenklappe. Langenbecks Arch. kli. Chir. 316:800, 1966.
10. Bowsker, D. R.: Cerebrospinal fl id dynamics health and disease, Springfield, Ill., 1960, Charles C Thomas, Publisher.
11. D vies, H., Lessof, M. H., Roberts, C. J., and Ross, D. N.: Homograft replacement of the aortic valve. Lancet 1:926, 1965.
12. Durra, C. G., and Gunning, A. J.: Heterologous aortic alve transplantation in the dog. Lancet 2:114, 1965.
13. Grote, W.: Gehirnpulsationen und Liquordynamik, Wien New York, 1964, Springer Verlag.
14. Hirsch, H. H., and Hanke, H.: Über das Verhalten von äthylenoxyd-sterilisiertem homologen Aortenklappengewebe in der Blutbahn, Langenbecks Arch. klin. Chir. 308:811, 1964.
15. Hirsch, H. H., and Flemming, H.: Thoraxchir.
16. Hogan, M. J., and Zimmerman, L. E.: Ophthalmic pathology. An atlas and textbook, ed. 2, Philadelphia, 1962, W. B. Saunders Compa y.
17. H bka, M., Šiška, K., Brozman, von., and Holec, V.: Replacement of mitral and tricuspidal valves by m tral homografts, J. Thoracic & Cardiovas. Surg. 51:195, 1966.
18. Hudson, R. E. B.: Pathology of the human ortic valve homograft, Brit. Heart J. 28:291, 1966.
19. Huber, B.: Personal communication.
20. Hill, Ch. E. R., and Castroviejo, R.: Present status of corneal transplant surgery. Tr. Am. Acad. Ophth. & Otol. 67:293, 1963.
21. Lam, C. R., Aram, H. H., and Munnell, E. R.: An experimental study of aortic valve homografts, Surg. Gynec. & Obst. 94:129, 1952.
22. M tz, H.: Personal communication.
23. Murray, G., Roschlau, W., nd Lougheed, W.: Homologous aortic valve-segment transplants as surgical treatment for aortic and mitral insufficiency. Angiology 7:466, 1956.
24. Murra, G.: Aortic valve transpla ts, Angiology 11:99, 1960.
25. O'Brien, N. F., and Gerbode, F.: Homotransplantation of the mitral valve, J. Surg. 31:81, 1964.
26. Payrau, P., Pouliquen, Y., and Faure, J. P.: Hétérogreffes de la cornée. Étude expérimentale t premiers résult ts hniques, An Ocul. 194:1, 1961.
27. Ross, D. N.: Homograft replacement of the aortic valve, Lancet 2:487, 1962.
28. Ross, D. N.: Surgical reconstruction of the aortic valve. Lancet 1:571, 1963.
29. Ross, D. N.: Homotranspla tation of the aortic valve in the subcoronary position. J. Thoracic & Cardiovas. Surg. 47:713, 1964.
30. Ross, D. N.: Aortenklappenersatz mit Homoiotransplantaten, Med. Klin. 22:931, 1966.
31. Ross, D. N.: Aortic valve replacement. Lancet 2:461, 1966.

Dynamic electrocardiography with strenuous exertion at high altitudes

Since the development of compact recording instruments, dynamic electrocardiography has become possible. This study compares the effects of high altitude, cold temperature, and strenuous exertion on nonacclimated, nonconditioned subjects with those on acclimated, conditioned skiers. I addition, we hope to demonstrat the practicality and technical feasibility of record ng continuous myocardial electrical activity during vigorous physical activity. Skiing was selected as the activity because of the physical exertion involved, the cold limate and the high altitude under which this sport is performed, and because of the increased public interest

Supported by United States Public Health Service Grant FR 5357-06.

Table I

Subject	Heart rate/min.			QT interval (sec.) $\frac{QT}{\sqrt{RR}}$			High altitude-exertion	
	Sea level resting	High altitude		Sea level resting	High altitude		Before	After
		Resting	Max		Resting	Max		
A. T	—	68	140	—	0 435	0 404	100/54	127/100
M D	—	78	174	—	0 445	0 441	118/88	127/95
R. B	—	78	158	—	0 434	0 435	147/100	148/98
W M	—	104	160	—	0 425	0 425	138/90	138/90
L P	78	106	165	0 420	0 436	0 475	148/113	147/102
W L.	75	126	162	0 408	0 428	0 485	127/80	132/90
J L.	68	120	166	0 420	0 462	0 460	128/82	132/92

in this sport. For the beginner the physical exertion required is near maximal and even more if one is unacclimated

The experiments were carried out t Arapahoe Basin near Loveland Pass in the Colorado Rocky Mou tains at altitudes of 10,000 to 11,500 feet. The recordings were done within four days after arrival. Seven subjects were selected. Two were conditioned acclimated ski instructors ges 34 (A. T) and 54 (M. D). One subject (W M), an oral surgeon age 42 lived t an altitude of 6,200 feet and was an experienced skier in fair physical condition. One subject (R B), university professor age 48 lived t 3 725 feet and was an experienced skier but had recently skied only once year The other three were selected to represent the verage unconditioned, nonacclimated novice skier These included J L., 43-year-old physician, W L., 36-year-old mercha t, and L. P 32 year-old physician. None of the subjects had any history of heart trouble, except for L. P who had history of rheumatic fever t age four but no know cardiac involvement. All had normal resting 12 lead electrocardiograms.

The equipment used was that developed by Holter The electrocardiorecorder weighing only 3½ pounds, was strapped to the skiers backs and bipolar electrodes ere attached to the subjects chests i the CM position[4] for continuous monitoring Continuous ECG monitoring was done hile resting and while skiing The moni oring was continued for at least 15 minutes after completion of skiing until the heart rate had stabilized and returned to resting levels. The tapes were scanned with the electrocardioscanner and representative tracings ere printed out by the harter I terpretations of the changes ere guided by the previous ork of Gilson[5] and Bruce.

The heart rat QT interval, and blood pressures are tabulated in Table I The nonacclimated individuals consistently had tachycardia but ere unable to accelerat their heart rates abov 170 per minute with exercise. Conversely those acclimated and conditioned had a slow resting heart rate and could increase their rate even though their exertion was not as strenuous There was no significant change in PR interval or QRS complex. The QT interval was prolonged (using K = 0 425 as upper limits) in all individuals in the resting state. The interval became markedly prolonged in subjects L. P W L., and J L during exertion. W L. became confused during maximal exertion at the time the QT interval measured 0 485 sec The T waves varied considerably but the usual change was for the mean xis to become more orientated toward the mean QRS xis and to become more peaked No significant ST changes occurred. Premature *ventricular* contractions occurred in four of the seven participants. R. B had runs of quadrigeminy J L. had one episode of multiple P V C. with some P.A.C. The other tw (W M and W L) had only occasional unifocal P V C s. W M P V C. occurred only after resting following 2 hours of rather vigorous exertion. As seen in Table I here are no significant changes in blood pressure. L. P whose blood pressure normally was 120/80 t sea level, experienced an elevated resting blood pressure throughou the four days A pulsus paradoxus of 14 mm. Hg in L. P was an interesting incidental finding

Dynamic electrocardiography i mountain climbing has demonstrated the feasibility of doing these recordings under ad erse conditions. This is supported by our studies in that the tracings made from the tapes during very strenuous activity are quite legible.

Pryor and associates and Peñaloza and associates ha show that ECG changes in people living at high altitudes generally show tendency for the mean QRS axis to shift to the right. Cardiac response nd other physiologic responses to altitude are reviewed by Balke. The resting tachycardia t high altitudes was expected. The inability to accelerat the heart rat which is rarely doubled[4] during a

period of decreased oxygen supply was anticipated. The atrial and ventricular ectopic beats were frequent in the unacclimated and nonconditioned group. Except in J. L. they were unifocal in origin. The significance of this increase in myocardial "irritability" is not known. The prolonged QT interval has been noted by others[8] and perhaps is related to hyperventilation. In those unacclimated prolongation was greater. As Balke[8] states, there was not typical response of blood pressure to hypoxia. The relationship of the elevated diastolic blood pressure seen in some of the subjects and the elevation of plasma catecholamines seen in high altitude situations is not clearly defined.[12] The pulsus paradoxus was unexpected but perhaps is explained by the pulmonary hypertension caused by the high altitude.

It is apparent that the physiologic and electrocardiographic responses in nonconditioned nonacclimated individuals are much greater than in their experienced counterparts. Whether this kind of activity is potentially dangerous in coronary prone individual is not known. On the contrary Balke and co-workers[13] raise the question as to the value of moderate altitudes with proper activity in the battle against coronary heart disease. With more people leading sedentary lives and attempting annual or biannual activity of this type, the potential dangers of such activities should be carefully scrutinized. The importance of acclimatization and prior physical conditioning before attempting such rigorous tasks also needs further evaluation. The physician's ability to advise wisely on such matters will await better understanding of physiologic data obtained during the actual performance of such activity.

Lenard L. Politte, M.D.
Carl H. Almond, M.D.
John T. Logue, M.D.
Departments of Medicine and Surgery
University of Missouri
Columbia, Mo.

*Present address: Madigan General Hospital, Tacoma, Wash.

REFERENCES

1. Holter, N. J.: New methods for heart studies, Science 134:1214, 1961.
2. Blackburn, H., et al.: A systemic comparison of chest lead configuration employed for monitoring during exercise, *in* Karvonen, M. J., and Barry, A. J., editors: Physical activity and the heart, Springfield, Ill., 1966, Charles C Thomas, Publisher, p. 101.
3. Gibson, J. S.: Electrocardiorecorder AVSEP pattern in 37 normal adult men, Am. J. Cardiol. 16:789, 1965.
4. Bruce, R. A.: Comparative prevalence of segmental ST depression after maximal exercise in healthy men in Seattle and Taipei, *in* Karvonen, M. J., and Barry, A. J., editors: Activity of the heart, Springfield, Ill., 1966, Charles C Thomas, Publisher, p. 144.
5. Sanders, J. S., and Martt, J. M.: Dynamic electrocardiography at high altitude, Arch. Int. Med. 118:132, 1966.
6. Pryor, R., Weaver, W. F., and Blount, G. S.: Electrocardiographic observations of 493 residents living at high altitudes (10,150 ft.), Am. J. Cardiol. 16:494, 1965.
7. Peñaloza, D., Gamboa, R., Marticorena, E., Echevarría, M., Dyer, J., and Gutierrez, E.: The influence of high altitudes on the electrical activity of the heart, Am. Heart J. 61:101, 1961.
8. Balke, B.: Cardiac performance in relation to altitude, Am. J. Cardiol. 14:796, 1964.
9. Asmussen, E., and Consolazio, F. C.: The circulation in rest and work on Mount Evans (4,300 M.), J. Physiol. 132:555, 1941.
10. Green, C. W., and Gilbert, N. C.: Studies on the responses of the circulation to low oxygen tension. III. Changes in the pacemaker and in conduction during extreme oxygen want as shown in the human electrocardiogram, Arch. Int. Med. 27:517, 1921.
11. Singh, J.: High-altitude pulmonary hypertension, Am. Heart J. 71:841, 1966.
12. Cunningham, W. L., Becker, E. J., and Kreuzer, F.: Catecholamines in plasma and urine at high altitudes, J. Appl. Physiol. 20:607, 1965.
13. Balke, B., Nagle, F. J., and Daniels, J.: Altitude and maximum performance in work and sports activity, J.A.M.A. 194:646, 1965.

The occurrence of a normal electrocardiogram after myocardial infarction

The more we know about the limitations of the electrocardiogram (ECG) the more it will justify its prominence in the assessment of physical health. In particular it is important to remember that a normal ECG may be found in the presence of acute or long-standing myocardial infarction.

It is common experience that in acute myocardial infarction the early ECG may be normal and it is only some days later that the pattern of acute infarction appears.

Recently cases have been reported in which the ECG showed typical infarction changes initially but at some time in the acute phase became transiently normal or showed marked lessening of the abnormalities. This was called the "intermediate phase of the ECG." In this study no criteria were

given for myocardial infarction and it is possible that some patients were suffering from acute coronary insufficiency with its well-recognized ECG fluctuations. Further studies of serial ECG changes during the acute phase will soon be forthcoming from coronary care units and may elucidate the diagnostic hazards of the "intermediate phase."

The standard ECG may remain normal throughout the course of acute myocardial infarction and recovery. The true incidence of such normal tracings is not surprisingly unknown. The absence of ECG signs is probably due either to the infarct being too small to cause changes or to its being placed far from the electrodes, for example high up posteriorly. Subscapular, esophageal, or high anterior chest leads may detect some of these infarctions.

In 1948, East and Oram[8] showed that some of the abnormal ECG wave forms may disappear following the typical changes which had accompanied an acute infarction. Further studies all report that the ECG may revert to normal after myocardial infarction but have shown a wide variation in the frequency of this change. Andersen and Skjaeggestad found 2 per cent of patients to have normal ECG's at 6 to 24 months and Pappas[9] found a similar incidence. Other workers found that 6 per cent of patients with transmural infarcts and 34 per cent with nontransmural infarcts in one series and 10 and 34 per cent, respectively, in another[4] had normal ECG's at about three years. Unfortunately, although criteria for myocardial infarction have usually been recorded, the criteria for a normal ECG have not. This, together with the observer error and variation known to occur in the conventional reporting of ECG's, increases the difficulty of interpreting these results and probably explains their differences.

The technique of measuring ECG waves has been used to define the normal ECG in order to make the concept more objective. Unfortunately, this technique is also subject to observer error and variation.[14]

The measurement technique was used in a recent study of 175 middle-aged men followed annually for up to four years after a first and definite myocardial infarction. The criteria for normality of the ECG were largely derived from Simonson's[16] study of 424 healthy white middle-aged men and from the Minnesota Code. At one year 10 per cent and at four years 20 per cent had normal ECG's. Of the 142 who had Q wave change infarction, 6 per cent developed a normal ECG. Of these one eighth were normal at three months, half at one year, and ECG's were still changing at four years. Other workers have found that there is no significant lessening of the ECG abnormalities after one year.[4,8] Of the 33 who had ST-T wave change infarcts, 54 per cent developed a normal ECG and of these one third had become normal by three months and four fifths by one year.

Of those with Q wave change infarction, the Q wave became normal in 13 per cent compared with the 30 per cent incidence over three years found by Kaplan and Berkson. There was no significant difference in the frequency of return to normal between anterior and posterior infarctions and the incidence of reinfarction was the same in those whose ECG did and did not return to normal, agreeing with previous reports.[8]

These results should be interpreted in the light of the method of patient selection used; for example, patients who developed complications such as heart failure, severe hypertension, or other diseases which might affect the ECG, who had a recurrence of infarction, or who died were excluded from the time of their last annual ECG.

A considerable proportion of patients with myocardial infarction will develop ECG's which, while not normal, are no longer diagnostic of myocardial infarction. It is known that over 70 per cent of patients with acute myocardial infarction admitted to the hospital show diagnostic changes on the ECG in the acute stage.[14] This percentage falls as time passes after infarction, and in one series 82 per cent had diagnostic ECG's in the acute stage, this figure falling to 69 per cent 6 to 24 months later. Evidence from a study of patients who did not die of ischemic heart disease but in whom a single old infarct was found at necropsy showed that ECG's taken in the month before death were diagnostic of myocardial infarction in only 35 per cent. A consecutive necropsy series based on the World Health Organization (1959) criteria for infarction on the ECG found that only 27 per cent of single old infarcts could be diagnosed on the ECG taken shortly before death.[17]

A further difficulty in the diagnosis of myocardial infarction is that the proportion of myocardial infarctions detected in life which are silent (that is, clinically undiagnosed but detected on the ECG) is between 15 and 33 per cent.[19] Return to normal of the ECG may well be more frequent after silent than after overt infarction and it is not yet known how many cases of myocardial infarction are not detected in a study which records ECG's only annually or biennially.

The standard ECG may be normal throughout the course of a myocardial infarction or there may be delay in the development of abnormalities. Once developed, the abnormalities may transiently diminish or disappear in the first few weeks and finally the ECG may become permanently normal as soon as a few months or as long as four years later.

One year after myocardial infarction as many as 10 per cent of the patients may have a normal ECG; a further 20 per cent may have ECG's no longer diagnostic of infarction, and some silent infarctions will not have been detected. Prevalence studies therefore considerably underestimate the incidence of detectable myocardial infarction unless ECG's are taken more frequently than annually. To this difficulty must be added that of the infarct which is not detectable clinically or on the ECG.

C. J. Burns-Cox, M.B., M.R.C.P.(Lond.)
University College Hospital
London, W.C.1, England

REFERENCES

1. Solomon, R. B., and Shapiro, H. H.: The electrocardiographic intermediate phase of an acute myocardial infarction, AM. HEART J. 71:582, 1966

2. East, T and Oram, S Cardiac pai with recovery of the T w ve Brit. Heart J 10:263, 1948
3. Andersen N nd Skjaeggestad Ö The lectrocardiogr m in patient w th previous myocardial farction, Acta med. scand nav 176 123, 1964
4. P ppas M P Disappearance of pathological Q w ves after cardiac infarction, Brit. Heart J 20 123 1958.
5. Kaplan, B M nd Berkson, D M Serial lectrocardiograms after myocardial infarction A Int Med. 60:430, 1964
6. Malmcrona, R Soderholm B, Bjorntorp, P Th lesius, O nd Heyman, F Myocardial infarction in the younger age groups. II Follow up observ tions w th special reference t pacity for work, Acta med. scandinav (Kobenhavn) 171(fasc 1) 59 1962.
7. D vies L G Observer variations in reports on lectrocardiograms, B it Heart J 20 153, 1958
8. Acheson, R. M Observer error nd variation in the interpretation of electrocardiograms in epidemiological study of coronary heart disease, Brit J Prev Soc. Med. 14:99 1960.
9. Higgins, I T T Kannel, W B and D wber T R The electrocardiogr m in epidemiological studies. Reproducibility validity and ternational comparison, Brit J Prev Soc. Med 19:53 1965
10. Rose, G A The oding of survey electrocardiograms by technicians Brit. Heart J 27:595 1965.
11. Burns-Cox, C J The return t normal of the electrocardiogram after myocardial infarction Lancet 1 1194 1967
12. Simonson, E.: The differentiation between normal and abnormal in electrocardiography St. Louis, 1961 The C. V Mosby Company Chap. 7
13. Blackburn, H W Keys, A., Simonson, E., Rautaharju, P and Punsar S The electrocardiogram in population tudies: classification system Circulation 21 1160, 1960.
14. Bohm, C Über elektrokardiographische Spät veränderungen nach Herzinfarkten, Med. Welt (Berl.) 13 798, 1962
15. Shanoff H M., and Little J A. Studies of male urvivors of myocardial infarction. VIII The electrocardiogram and ten year survival, Am J Cardiol 18:535, 1966.
16. Skjaeggestad, Ö and Molne K. The electrocardiogram in patients w th healed myocardial i farction disclosed t utopsy Acta med. scandinav 179:23 1966.
17. Woods, J D Laurie W nd Sm th, W G: The reliability of the electrocardiogram in myocardial infarction, Lancet 2:265 1963
18. Morris, J N Kagan, A. P tison, D C., Gardner M J and Raffle, P A. B Incidence and prediction of ischaemic heart disease in London busmen, Lancet 2:553, 1966.
19. Rosenman, R H Friedman, M Straus R., Wurm M Jenkins, D Messinger H B., Kositchek, R Hahn W and Werthessen, N T Coronary heart disease in the Western collaborative group tudy—a follow-up experience of 2 years, J A. M A. 195:86, 1966.

Letters to the Editor

Reply to Dr Voigt

To the Editor

Dr Voigt stresses the beneficial effects of steroid therapy in myocarditis especially of viral etiology. As our article indicated, we also feel steroids to be of great value in selected cases. We did, indeed, hedge as to what the specific indications were, first because it was not primarily a report on therapy and second because we are not sure that clear-cut indications are presently defined. Our caution in using steroids with systemic viral disease is based on the clinical experience in certain pediatric cases, in the patients with altered immune mechanisms—especially those with leukemia—to which Dr Voigt alluded, and in the treatment of viral keratitis. The latter group is primarily due to herpes simplex, a viral etiology which was presented in some depth. Added to this is our ignorance of that point in the pathophysiology of myocarditis when the cardiac insult ceases to be due to the pathogen and becomes more related perhaps to a host immunologic phenomenon as in rheumatic myocarditis. Steroids at one point may prevent a necessary inflammatory response to a direct parasitemia and early healing of the diseased myocardium. Yet steroids may prevent inflammation from encroaching on the cardiac conduction system and the predisposition of these patients to arrhythmia or later suppress the smoldering inflammation seen in the rheumatic type.

With these reservations we then stress Dr Voigt final statement that patients with strongly suspected viral myocarditis *who do not respond to the usual therapeutic measures directed against heart failure* should receive a trial of steroids.

Randall W. Bell, Major, MC, USA
William Murphy, Lieutenant Colonel, MC, USA
Walter Reed General Hospital
Walter Reed Army Medical Center
Washington, D C 20012

Steroid therapy in viral myocarditis

To the Editor

In the article *Myocarditis in young military personnel* by Drs. Bell and Murphy (AMERICAN HEART JOURNAL 74:309, 1967), the question of the use of adrenocorticosteroid therapy in acute myocarditis of viral etiology is raised. Reference is made to reports reviewing the contraindications of steroid therapy in viral disease although the authors seem to feel that drugs with anti-inflammatory properties may be desirable. The data are sparse but there are several reports of patients with acute, nonrheumatic myocarditis whose rapidly deteriorating course was abruptly reversed concomitant with the institution of steroid therapy.[1-4] We have observed one patient, a young man with rapidly progressive heart failure clinically due to acute myocarditis, who recovered quickly with steroid therapy. On later study he had a normal cardiac catheterization and normal left ventricular function under angiotensin stress.[5] A viral etiology for the myocarditis was not confirmed, as is often the case in such patients.

Fear of instituting steroid therapy in patients with viral myocarditis probably stems from the observations that patients in whom immune mechanisms are seriously suppressed, such as patients with leukemia, lymphomas, and carcinoma, who have been treated with steroids and/or antitumor drugs, occasionally die of or with overwhelming viral infection. Histologic examination reveals involvement of many organs, including the heart and adrenal glands. Also, overwhelming varicella infection in children being treated with cortisone for other diseases has been described. However, steroids are recommended by some investigators in patients with varicella pneumonia and encephalitis, and beneficial results have been reported.

Clinical evidence that further dissemination of virus occurs in patients treated with steroids after the onset of viral myocarditis has not, to my knowledge, been observed. Actually, at the time a patient presents with clinical acute myocarditis, the virus is probably already widely disseminated. It seems logical that the tissue reaction to the virus is in large part responsible for the myocardial dysfunction and heart failure, and that the salutary effect of steroids in these patients may be due to their anti-inflammatory properties.

The statement that cortisone has been shown to interfere with viral replication is not quite accurate. In the work to which the authors refer, it was shown that in chick embryos infected with influenza virus, cortisone suppressed the synthesis and release of *interferon* and earlier observations showed that the yield of virus from similar preparations was *increased* by the addition of cortisone. These authors suggested that the effect of cortisone on interferon might be due to retardation of protein synthesis. The application of these observations to clinical situations is certainly not clear but it would appear from clinical experience that patients with acute myocarditis presumably secondary to viral infection, who do not respond to the usual therapeutic measures directed against heart failure, should receive a trial of steroids.

Gunter C. Voigt, M.D.
The Johns Hopkins Hospital
Baltimore, Md. 21205

REFERENCES

1 Garrison, R F od Swibber R. C Myocarditis of unknown etiology (Fiedler' ?) treated with ACTH J Pediat 42:591 1953
2 Seg I J I Harvey W P and Gurel, T Diagnosis and treatment of primary myocardial disease Circulation 32:837 1965
3 Anger I F Acute septic myocarditis corticosteroid therapy J Pediat 64 716, 1964
4 Voigt G C and Lewis K B Idiopathic myocardiopathy Maryland State M J June-July 1966
5 Zacherle B J and Marshall, R. M : Personal communication
6 Harrison T R Principles of internal medicine, New York, 1966, McGraw-Hill Book Company Inc p. 1736.
7 Kilbourne E. D Smart K. M and Pokorny B A. Inhibition by cortisone of the synthesis nd action of interferon, N ture 190:650, 1961

√Book reviews

KREISLAUFSTILLSTAND UND WIEDERBELEBUNG. By Dr med. Martin Stauch, Stuttgart, 1967 Georg Thieme Verlag, 80 pages.

This small manual on cardiac resuscitation is well written, profusely illustrated, and nicely organized The booklet is pocket-sized. Dr Stauch discusses the indications for the diagnosis of cardiac arrest, ventilation, techniques, and management including the use of drugs. This is good book which should be useful to nurses, students, and physicians.

ENCYCLOPEDIA OF MEDICAL RADIOLOGY Part 4 Roentgen Diagnosis of the Heart and Blood Vessels. By F Loogen, R Rippert, J Schoenmackers, and H Vieten, Berlin, Heidelberg, New York, 1967 Springer Verlag, 518 pages. Price $45 00

This volume is an excellent presentation of the role of roentgenology in the diagnosis of cardiac and blood vessel disease The illustrations are very good and numerous. There is good index and bibliography The binding is excellent and so is the printing, both so characteristic of German publications today The presentation is primarily designed and intended for the practicing physician. This volume should not only interest radiologists, but should be very useful to cardiologists and internists as well as cardiac surgeons. This is very good volume in the series of encyclopedia of medical radiology

BLOOD CLOTTING ENZYMOLOGY Edited by Walter H. Seegers, New York and London, 1967 Academic Press, Inc 628 pages. Price $27 50.

This is an excellent and authoritative presentation on blood coagulation The contributors are authorities in their field and they have written excellent chapters. The illustrations and bibliographies are good and so are the printing and index. Among the subjects discussed are use and regulation of the blood clotting mechanisms molecular characteristics of substances active in blood coagulation, activation of prothrombin, fibrinogen to fibrin transformation, immunochemistry surface activity blood coagulation, antithrombin, plasma anticoagulants or inhibitors, platelets in hemostasis, irregular blood coagulation, ultrastructure of the fibrin clot, and chemistry and function of vitamin K. These important subjects, of course, do not include all the factors involved in blood clotting but they represent extremely important ones This book is highly recommended on the subject of blood clotting, not only hematologists but medical student and physicians in general

CLINICAL VECTORCARDIOGRAPHY By Te-Chuan Chou M D and Robert A. Helm, M.D New York and London, 1967 Grune & Stratton Inc., 314 pages. Price $12.50.

This is a well written and useful book on vectorcardiography The authors introduce the concept well and present the theories in a simple and easy to understand fashion. They discuss some of the SVCG in the major cardiac disease states. The illustrations are clear and well selected. There is a rather extensive and useful section on "Exercises in Vectorcardiography in which the SVCG and electrocardiogram (ECG) are illustrated and supported by an interpretation and clinical data. This book should not only be useful to students and cardiologists, but to anyone who wishes to learn vectorcardiography

BALLISTOCARDIOGRAPHY AND CARDIAC PERFORMANCE Edited by Abraham Noordergraaf and Gerald H Pollack, St. Louis, M Warren H Green, Inc 150 pages. Price $9 25

These are the proceedings of the eleventh annual meeting of the Ballistocardiography Research Society held in Atlantic City on April 30 1966. As with any proceedings the papers should vary in interest among readers. The papers include selected aspects of the field. This book should interest cardiologists and others who are working with the BCG in research and clinical medicine.

ASPECTS NEURO-PSYCHIATRIQUES DE LA CHIRURGIE CARDIAQUE À CŒUR OUVERT By Luc Picard Chef de Clinique de Neurologie, Assistant des Hôpitaux Paris 1967 Editions Doin, Deren & Cie 283 pages.

This book on the neuropsychiatric aspects of open heart operation summarizes in French the problems and experimental and clinical studies of the changes in cerebral function in patients who undergo open heart operation. The problems of anoxia, drugs, cerebral embolization electroencephalogram (EEG) changes anesthesia, and hypothermia are discussed There is fairly extensive bibliography of 837 references. The discussions are primarily from the point of view of the neurologist and psychiatrist This is an important subject which needs more study and consideration in cardiology and cardiac operation. This book provides in one source aspects of the central nervous system problems of open cardiac operation and provokes thought and source of ideas for future research

Announcement

THE THIRD INTERNATIONAL SYMPOSIUM ON DRUGS AFFECTING LIPID METABOLISM will be held Milan, Italy from Sept 9 to 11 1968. The Joint Scientific Secretaries are D W. L. Holmes, The Lankenau Hospital Philadelphia, Pa. 19151 and Prof R P oletti Institute of Pharmacology of the University of Milan The sessions will be divided as follows Drugs affecting (1) FFA mobilization; (2) Triglycerides; (3) Cholesterol nd bile acid metabolism (4) Serum lipoproteins (5) Tissue lipids and obesity (6) General. For further information contact. Miss H J Prain, Institute of Pharmacology University of Milan, Via A. del Sarto 21 20129 Milan, Italy

American Heart Journal

May 1967 Volume 73 Number 5

Editorial

The value of direct current conversion of atrial fibrillation

M. E. Scott, B.Sc., M.B., M.R.C.P.
J. F. Pantridge, M.C., M.D., F.R.C.P.
Belfast, Northern Ireland

The introduction of synchronized direct current (D.C.) shock as a method of removing atrial fibrillation represented a major therapeutic advance. Since this method has been used in several thousands of centers throughout the world, and since experience has accumulated over a five year period, it is now appropriate to review the value of the procedure.

There are many advantages to be derived from the restoration of sinus rhythm. Most patients feel better, exercise tolerance is improved, and palpitation, particularly on exertion, is removed. The heart rate is again brought under the sensitive control of the autonomic nervous system, and the exaggerated tachycardia on exercise is prevented. Maintenance of sinus rhythm diminishes the risk of embolism[2] which is said to occur in at least 20 per cent of all patients with chronic atrial fibrillation.

There has been some lack of agreement on the effect of restoration of sinus rhythm on cardiac output. Some workers report that the output is unaffected. The majority have found a significant rise after removal of the arrhythmia.[3] We have made serial measurements of cardiac output after D.C. conversion. While there was usually no rise in resting output within three hours of successful conversion, the output did show a significant rise when estimated three days later.

The evidence indicates that synchronized D.C. shock is safer, more effective, and more convenient than drug conversion using quinidine.[4] The risk of quinidine conversion is well known. A mortality rate of 2 to 4 per cent from sudden cardiovascular collapse has been reported.[illegible] Synchronized D.C. conversion, in contrast, is safe. Lown's prediction in 1964[illegible] that "the major complication following cardioversion will result not from the procedure, but from the drugs utilized to sustain sinus rhythm," has been confirmed by our experience in 578 attempted conversions in 356 patients. We have had no serious complication from the procedure, but one death resulted from quinidine used to maintain sinus rhythm. Instances of the precipitation of serious ventricular arrhythmia have been reported.[illegible] These have resulted from improper synchronization or from digitalis or quinidine intoxication. Nodal bradycardia giving rise to Stokes-Adams attacks has been recorded.[illegible]

From the Royal Victoria Hospital, Belfast, Northern Ireland.

This bradycardia responded to atropine. It was thought that nodal bradycardia resulted from overdigitalization. It is now the practice to discontinue digitalis two days before attempted conversion.

The technique of D.C. conversion has been improved by the placing of the electrodes in the anteroposterior position. Recently it has been suggested that further improvement may be obtained by the use of an esophageal electrode.

Anticoagulant therapy prior to D.C. conversion is advocated by some workers.[2] We have not employed routine anticoagulant therapy and in the week following 450 successful conversions, only two embolic episodes, both minor, were noted. Studies have been made of the incidence of emboli in anticoagulated and nonanticoagulated patients. No difference was found.[34] We would agree with Lown's suggestion that the use of anticoagulants be limited to two high risk groups, namely patients who have had recent or recurrent embolism and women with asymptomatic mitral valve disease having atrial fibrillation of recent onset. Pulmonary edema may occasionally develop following conversion.[33] Embolism from the right atrium has been suggested as the mechanism and in one instance anticoagulation prevented the recurrence of this complication.

It is clear that synchronized D.C. shock will remove atrial fibrillation in a higher proportion of patients than will quinidine. The conversion rate for quinidine was 50 to 60 per cent,[33] whereas for D.C. conversion the rate is 76 to 94 per cent.[34] McDonald and his colleagues[33] demonstrated most strikingly the superiority of D.C. shock over quinidine. They succeeded in establishing sinus rhythm in 43 of 50 patients who had failed to convert with quinidine. In our experience the chances of conversion are similar whether the atrial fibrillation results from rheumatic, ischemic, or thyrotoxic heart disease. However, "lone" or idiopathic atrial fibrillation is associated with a lower conversion rate. The duration of the atrial fibrillation is the important factor influencing the chance of successful conversion. The presence of a large left atrium, predominant mitral incompetence, and small fibrillary "f" waves in V1 of the cardiogram diminish the chances of successful conversion probably because of their association with longstanding atrial fibrillation.[33]

Unfortunately, while it is usually easy to remove atrial fibrillation, it is difficult to maintain sinus rhythm. The relapse rate is high. In a long term follow-up of 287 patients we found that although the relapse rate diminished markedly after the first three months, only 41 per cent remained in sinus rhythm one year after conversion and 20 per cent after three years.[34] In our experience the etiology of the arrhythmia has an effect on the incidence of relapse. When patients with treated thyrotoxicosis were compared with those whose atrial fibrillation resulted from ischemic heart disease, it was found that the former were more than twice as likely to maintain sinus rhythm following conversion. Patients with rheumatic heart disease occupied an intermediate position.

We did not find that either quinidine in a dose of 1.2 Gm. daily or oral potassium in a dose of 50 mEq. daily effected a significant reduction in the relapse rate.[35] However, many workers use quinidine in an attempt to prevent recurrence of the arrhythmia,[36] and it has been suggested that the inability to tolerate maintenance doses of quinidine is a contraindication to attempted D.C. conversion.[2]

Patients under our care who were not on maintenance therapy showed a relapse rate not substantially different from that reported by workers who use maintenance quinidine.[2,36] The relapse rate following conversion with quinidine was also high.[33,37]

Repeated conversions with quinidine were not often performed because of the greater hazards involved. The safety and convenience of conversion by D.C. countershock introduced the possibility of reconverting patients who relapse after maintaining sinus rhythm for a reasonable period. A total of 92 per cent of our attempted second and 87 per cent of our attempted third conversions were successful. We have followed 86 patients for one year after an attempted second D.C. conversion. In those patients who had maintained sinus rhythm for six months or more following the first conversion there was a 100 per cent reconversion rate and more than 30 per cent were still in sinus

rhythm one year after the second conversion. In those who had relapsed within six months of their first conversion 86 per cent converted on the second attempt and of these only 11 per cent remained in sinus rhythm one year later. It would appear, therefore, that repeat D.C. conversion is justified in patients who have maintained sinus rhythm for six months or more after the first conversion. We have a substantial number of patients who are in sinus rhythm having required D.C. conversion at intervals of between 6 and 18 months over the past four years. The majority are not on drugs and are symptom-free.

It is thus clear that D.C. conversion is the method of choice in attempting to remove atrial fibrillation when this is indicated. When successful it confers demonstrable benefits. The outstanding problem is that of preventing relapse of the arrhythmia.

REFERENCES

1. Lown, B., Amarasingham, R., and Neuman, J.: New method of terminating cardiac arrhythmias. Use of synchronized capacitor discharge, J.A.M.A. 182:548, 1962.
2. Lown, B.: Electrical reversion of cardiac arrhythmias, Brit. Heart J. 29:467, 1967.
3. Pantridge, J. F., and Halmos, P. B.: Conversion of atrial fibrillation by direct current countershock, Brit. Heart J. 9:241, 1965.
4. Wetherbee, D. G., Brown, M. G., and Holzman, D.: Ventricular rate—response following exercise during atrial fibrillation, and after conversion to normal sinus rhythm, Am. J. M. Sc. 223:667, 1952.
5. Goldman, M. J.: The management of atrial fibrillation. Indications for and methods of conversion to sinus rhythm, Progr. Cardiovas. Dis. 2:465, 1960.
6. Graettinger, J. S., Carleton, R. A., and Muenster, J. J.: Circulatory consequences of changes in cardiac rhythm produced in patients by transthoracic direct-current shock, J. Clin. Invest. 43:2290, 1964.
7. Halmos, P. B., and Patterson, G. C.: The effect of atrial fibrillation on cardiac output, Brit. Heart J. 27:719, 1965.
8. Morris, J. J., Jr., Entman, M., North, W. C., Kong, Y., and McIntosh, H.: The changes in cardiac output with reversion of atrial fibrillation to sinus rhythm, Circulation 31:670, 1965.
9. Killip, T., and Baer, R. A.: Haemodynamic effects after reversion of atrial fibrillation to sinus rhythm by precordial shock, J. Clin. Invest. 45:658, 1966.
10. Scott, M. E., Patterson, G. C., and Pantridge, J. F.: Serial cardiac output estimations after D.C. conversion of atrial fibrillation. To be published.
11. Thompson, G. W.: Quinidine as a cause of sudden death, Circulation 14:757, 1956.
12. Lown, B.: "Cardioversion" of arrhythmias. (II) Mod. Conc. Cardiovas. Dis. 33:869, 1964.
13. Rabbino, M. D., Likoff, W., and Dreifus, L. S.: Complications and limitations of direct-current countershock, J.A.M.A. 190:417, 1964.
14. Castellanos, A., Jr., Lemberg, L., and Fonseca, E. J.: Ventricular arrhythmias after D.C. countershock, Am. Heart J. 70:583, 1965.
15. Halmos, P. B.: Direct current conversion of atrial fibrillation, Brit. Heart J. 28:302, 1966.
16. Lown, B., Kleiger, R., and Wolff, G.: The technique of cardioversion, Am. Heart J. 67:282, 1964.
17. Fields, J., Shachtman, J., Craig, S. D., Berkovits, B. V., and Roger, A.: Special electrode device for trans-esophageal cardioversion, Digest of 7th International Conference on Medical and Biological Engineering, Stockholm, 1967.
18. Duchelle, R. A.: Indications for conversion of atrial fibrillation to normal sinus rhythm, M. Clin. North America (No. 1) 50:117, 1966.
19. Killip, T.: Synchronized D.C. precordial shock for arrhythmias, J.A.M.A. 186:1, 1963.
20. Charms, B. L., Edelstein, J., Kamen, A., and Goldberg, A.: Direct current countershock. Long term follow-up, Dis. Chest 50:1, 1966.
21. Resnekov, L., and McDonald, L.: Pulmonary oedema following treatment of arrhythmias with direct current shock, Lancet 1:506, 1965.
22. Hay, J.: The action of quinidine in the treatment of heart disease, Lancet 2:543, 1924.
23. McDonald, L., Resnekov, L., and O'Brien, K.: Direct current shock in the treatment of drug-resistant cardiac arrhythmias, Brit. M. J. 1:1468, 1964.
24. Scott, M. E., Patterson, G. C., Geddes, J. S., and Pantridge, J. F.: The long-term results of D.C. conversion of atrial fibrillation. To be published.
25. Oram, S., and Davies, J. P. H.: Further experience of electrical conversion of atrial fibrillation to sinus rhythm. Analysis of 100 patients, Lancet 1:1294, 1964.
26. Rossi, M., and Lown, B.: The use of quinidine in cardioversion, Am. J. Cardiol. 19:234, 1966.
27. Sokolow, M.: The present status of therapy of the cardiac arrhythmias with quinidine, Am. Heart J. 42:771, 1951.

Clinical communications

A diastolic murmur in the healthy newborn infant

S. Zoe Walsh, M.D.
Stockholm, Sweden

The reported incidence of murmurs in newborn infants has increased over the years from 1.9 per cent[1] to almost 90 per cent on follow-up examinations. This must depend partly on increased frequency of examination by one or two interested observers, starting immediately after delivery, inclusion of faint murmurs, use of better listening and recording equipment, knowledge that continuous murmurs are audible in the newborn of various mammalian species, and possibly longer auscultation under better conditions in a greater number of areas. Although more recent studies show a higher incidence of systolic murmurs in newborn infants,[4] only Burnard has reported an isolated diastolic murmur which he tentatively ascribed to a venous hum.

The purpose of this paper is to report findings in four healthy newborn infants with diastolic murmurs, all of whom had early clamping of the umbilical cord, and to speculate about its etiology.

Method

Immediately after delivery, infants were taken to another room (temperature 23 to 25° C.) where they were kept well covered. All recordings, including 16-lead electrocardiograms (ECG's)* were taken by the author at a paper speed of 100 mm. per second with the 4-channel Mingograph 42 jet writer. This recorder permits simultaneous registration of three of the six high-pass filters whose nominal frequencies are at octave intervals—i.e., 12, 25, 50, 100, 200, and 400 c.p.s. The electrodynamic microphone has an internal diameter of 3 cm.

Clinical findings

Symptoms and physical signs. All four patients had a number of features in common and are therefore reviewed together. The principal features of each case are set out in Table I.

The mothers were healthy; three were primiparas aged 21 to 26 years old and one was a 40-year-old multipara. Pregnancy was uneventful and only nitrous oxide and/or trichloroethylene were administered intermittently for a maximum of one hour prior to normal delivery. Clamping of the cord was performed 1½ to 4 seconds after birth, prior to the first breath and spontaneous cry in three infants and concurrently with the first breath in one infant (E.). There were no signs of asphyxia.

On initial examination at an average age of 13¼ minutes, pallor was marked in two (S. and E.) and mild in two infants, and

From the Department of Pediatrics, Karolinska Hospital, and the Southern Maternity Hospital, Wollmar Yxkullsgatan 27, Stockholm, Sweden.
Supported by grants from the National Institutes of Health (1 TO HD 66-01), the American Heart Association, and the Association for Aid of Crippled Children.
Received for publication May 1, 1967.

*Standard bipolar, augmented unipolar, and precordial leads V, R, V ... V ... V ... (tip of xiphoid process), V... and V... (second right and left intercostal spaces at the sternal border).

there was no cyanosis. Three were very irritable while E. seemed unusually quiet and tended to whine on stimulation rather than cry. There was little change in these findings on subsequent examinations at mean ages of 26 and 45 minutes. At the time of appearance of the essentially isolated long variable diastolic murmur at mean age of 3½ hours, they were, on the whole, slightly warmer and pinker. In each case the murmur was localized to the first and second left intercostal spaces; it was poorly transmitted, tended to have a rather hollow quality, and was of Grade I-II/VI intensity. No ejection sound or separate apical murmur was heard. In three infants, the second heart sound was slightly accentuated and split. None had a waterhammer pulse but only the radial pulse was felt. Three infants had a systolic murmur of varying type in the pulmonic area on a previous examination but this was well heard only in T. At a mean age of 26 hours, irritability was no longer a striking feature and only T remained pale. The diastolic murmur was no longer audible; two infants had no murmur and two had a somewhat different systolic murmur than previously, i.e., slightly harsh midsystolic maximal at the mid and lower left sternal border. At the end of the week, hematocrits ranged from 43 to 51.3 per cent; two infants had no murmur; S. had a faint short localized pulmonary systolic murmur (Grade I/VI) which could not be recorded; and E. a squeaky superficial systolic murmur maximal at the midleft sternal border on auscultation but best seen at the apex on the phonocardiogram.

Phonocardiography. On initial examination the second sound was split 10 to 15 msec. and was less intense than the first heart sound in the pulmonic area in three infants. Only S had an inconstant variable early systolic murmur. At the time of the appearance of the diastolic murmur although no systolic murmur was detected on auscultation, three infants had a very short early systolic murmur in the same region. The second heart sound was now accentuated and splitting had increased in three infants. In all four infants the diastolic murmur was best seen in the high frequency ranges. It started immediately after the second heart sound and extended up to or beyond the first heart sound and varied presumably with respirations (Figs. 1 and 2). On the following day two infants (T. and L.) had a long pulmonary systolic murmur with midsystolic accentuation, and in all four infants, the second sound was accentuated and split 15 to 25 msec. At the end of the week only S. had a persistent early systolic murmur.

Electrocardiography. On initial examination heart rate and QRS electrical axis were within the expected range of normal values for this laboratory. Electrocardiographic intervals were shorter (P wave duration, P-R interval, and Q-Tc interval) but similar to those seen in other infants with early clamping of the cord. T. had the highest R_{V1} and deepest S_{V6} in a normal series of about 200 healthy infants of similar age. Only E. had an entirely upright T_{V1}. At the time of appearance of the diastolic murmur, comparison with earlier electrocardiographic tracings showed the main changes to be in Lead V_6, i.e., increased amplitude of the Q, R, and S waves and decreased amplitude of the T wave. However, there was a tendency for the highest R and S waves on both sides of the precordium to occur at or near the time of the appearance of this murmur. The mean amplitude of Q waves in Leads III and aVF was the same as in a comparable group of other infants who did not have a diastolic murmur.

Comment

The differential diagnosis of a transient diastolic murmur in the newborn infant includes venous hum, atrioventricular flow murmur, incompetent semilunar valve, and patent ductus arteriosus. *Venous hums* are usually continuous though maximal in diastole. They are best heard on the right side, more common in anemia, and might therefore be expected to occur in infants with early clamping of the cord. On the other hand, it is difficult to explain why only a diastolic murmur should be heard on the left side between two and four hours of age. A *flow murmur* arising at the atrioventricular valves from left-to-right shunting through either a stretched foramen ovale or a patent ductus generally causes a mid or late low-pitched diastolic murmur maximal in the mitral or tricuspid

Clinical communications

A diastolic murmur in the healthy newborn infant

S. Zoe Walsh, M.D.
Stockholm, Sweden

The reported incidence of murmurs in newborn infants has increased over the years from 1.9 per cent to almost 90 per cent on follow-up examinations. This must depend partly on increased frequency of examination by one or two interested observers, starting immediately after delivery, inclusion of faint murmurs, use of better listening and recording equipment, knowledge that continuous murmurs are audible in the newborn of various mammalian species, and possibly longer auscultation under better conditions in a greater number of areas. Although more recent studies show a higher incidence of systolic murmurs in newborn infants,[1-4] only Burnard[4] has reported an isolated diastolic murmur which he tentatively ascribed to a venous hum.

The purpose of this paper is to report findings in four healthy newborn infants with diastolic murmurs, all of whom had early clamping of the umbilical cord, and to speculate about its etiology.

Method

Immediately after delivery, infants were taken to another room (temperature 23 to 25° C.) where they were kept well covered. All recordings, including 16-lead electrocardiograms (ECG's),* were taken by the author at a paper speed of 100 mm. per second with the 4-channel Mingograph 42 jet writer. This recorder permits simultaneous registration of three of the six high pass filters whose nominal frequencies are at octave intervals—i.e., 12, 25, 50, 100, 200, and 400 c.p.s. The electrodynamic microphone has an internal diameter of 3 cm.

Clinical findings

Symptoms and physical signs. All four patients had a number of features in common and are therefore reviewed together. The principal features of each case are set out in Table I.

The mothers were healthy; three were primiparas aged 21 to 26 years old and one was a 40-year-old multipara. Pregnancy was uneventful and only nitrous oxide and/or trichloroethylene were administered intermittently for a maximum of one hour prior to normal delivery. Clamping of the cord was performed 1½ to 4 seconds after birth, prior to the first breath and spontaneous cry in three infants and concurrently with the first breath in one infant, E. There were no signs of asphyxia.

On initial examination at an average age of 13⅓ minutes, pallor was marked in two (S. and E.) and mild in two infants, and

From the Department of Pediatrics, Karolinska Hospital, and the Southern Maternity Hospital, Wollmar Yxkullsgatan 27, Stockholm, Sweden.

Supported by grants from the National Institutes of Health (1 TO1 HD 166-01), the American Heart Association and the Association for Aid to Crippled Children.

Received for publication May 1, 1967.

*Standard bipolar, augmented unipolar, and precordial leads V₃R, V₁ to V₆, [illegible], 2R and 2L (second right and left intercostal spaces at the sternal border).

Table I—Cont'd

					Electrocardiogram						
Rate	Axis	P dur (msec.)	P–R (msec.)	Q–T (msec.)	R_{V1} (1/10 mv.)	S_{V1} (1/10 mv.)	T_{V1} (1/10 mv.)	Q_6 (1/10 mv.)	R_{V6} (1/10 mv.)	S_{V6} (1/10 mv.)	T_{V6} (1/10 mv.)
136	+134.5	50	90	404	33	13	↓2 ↑½	—	4.5	14	↑1
118	+133.5	60	100								
125	+127	60	105	458	25	13	↓1½ ↑½	2.5	23	14	↑2
133	+137	50	90	367	29	12	↓1 ↑½	2.6	18	13.5	↑1½
118	+134	40	90	415	24.5	10.5	↓1 ↑3	2	20	18	↑2↓1?
171	—	40	80	399	23.5	7	↓4	2	18.8	16	↑3
154	+114	50	75	325	19	12	↓1½	1	6	5.5	↑½
150	+127.5	60	100								
146	+120	70	105	350	24	[illegible]	↓1 ↑½	0.5	4	8	↑½
125	+130	60	100	357	28.5	15.5	↓1 ↑½	3	11.8	8.8	↓½
130	+113	45	90	378	25.5	22	↓3	1.5	8	9	↑1½
184	+107	60	95	336	18	18	↓3	3	10	7	↑1½
148	−170.5	55	90	344	20	13.5	↓1 ↑2	—	—	4	—
120	−159	40	90								
108	−105	60	100	444	17.5	11	↓1 ↑2	0.5	3	5	↑½
118	+172	80	95	434	14	10	↓	0.5	3	4.5	↓1
138	131	50	100	457	18	3	↑1½	0.5	2.5	4.0	↑½
125	+140	40	90	390	13	6.5	↓2½ ↑1	1	8.8	4	↑2
113	+113	80	100	402	13	11	↑3	1	11	3	↑½
115	+90	45	105	422	15	17	↑3	0.5	10	5	↑½
139	+120	50	100	393	17	13	↑2½	—	12	6.5	↑1
136	+120	40	110	332	19	12	↓ ½	0.8	8	5	↑1
130	+136	30	100	342	13	7.5	↓3 ½	0.5	8	8.8	↑2½

expansion of the lungs, while systemic resistance rises after ligation of the umbilical cord. Blood then flows through the ductus arteriosus from the aorta into the pulmonary artery and contributes to persistent elevation of pulmonary artery pressure during the first hours of life. Thus, the left ventricle is exposed to a gradually decreasing diastolic overload while the right is exposed to a still more gradually decreasing systolic overload as pulmonary artery pressure falls.

The amount of blood transferred to the infant at the time of delivery determines to a large extent whether the infant has a smaller or larger blood volume. This in turn affects pulmonary and systemic pressures as well as other systems. Thus, infants with only a small placental transfusion after early clamping of the cord have an earlier drop in pulmonary artery pressure than do those with a large placental transfusion (late clamping of the cord). Pulmonary diastolic pressure decreases at a comparatively faster rate than does the systolic pressure and not uncommonly a diastolic pressure difference is present with nearly equivalent systolic

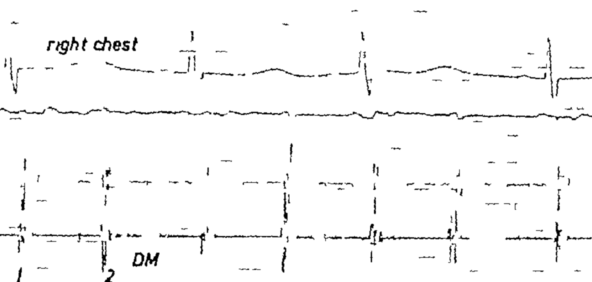


Fig. 1. Male infant (S.) with cord clamped at 4 seconds. Tracing taken at 4 hours of age in pulmonic area shows high frequency diastolic murmur. No early systolic murmur is present. Electrocardiographic lead taken over right chest. Recorded with gain 1/5, 12, 50, and 200 c.p.s. Distance between fine vertical lines = 10 msec.

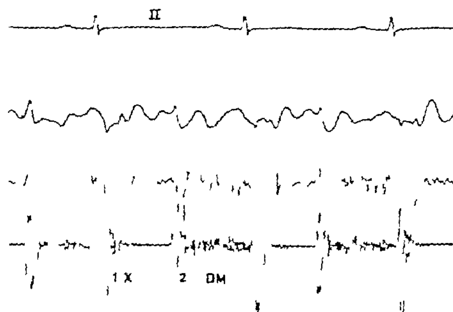


Fig. 2. Female infant (E.) with cord clamped at 2 seconds. Tracing taken at 4 hours of age in pulmonic area shows long diastolic murmur and possible early systolic murmur (X). Recorded with gain 1/2, 12, 50, and 200 c.p.s.

pressures in the pulmonary artery and descending aorta.[7] Indeed Emmanouilides and associates[8] noted that pulmonary diastolic pressure was uniformly lower than systemic diastolic pressure in most infants less than 10 hours of age. It is not known, however, whether the ductus closes earlier in early clamped infants, although electrocardiographic studies suggest that the load on the left ventricle may be comparatively less.

Experiments in lambs[19] indicate that

the intensity of the ductus murmur may vary considerably with respiration becoming much louder during expiration. These authors also point out that during systole blood enters the pulmonary trunk both from the right ventricle and from the ductus, but during diastole only from the ductus. Hence the pressure difference between the two ends of the ductus and therefore the rate of flow through it, would be expected to be greater during diastole

Emmanouilides and associates found that the majority of infants with negative T waves in V had a left to-right shunt through the ductus arteriosus and a higher pulmonary arterial pressure It is therefore of interest that, when the diastolic murmur became audible all four showed a decrease in T wave amplitude although only two had inverted T waves in this lead Moreover the main change from previous tracings was an increase in amplitude of Q R and S waves in this lead Furthermore the very largest amplitude R and S waves in leads from both sides of the precordium during the week occurred at about this time.

Although it is tempting to ascribe this murmur to flow through the ductus arteriosus partly because of its hollow ductal quality location, age of appearance and the electrocardiographic findings, there are several questions which must be asked.

Is there any relationship between time of clamping of the cord and appearance of this murmur?

As presumably all infants have transient left to-right shunting through the ductus arteriosus during the first hours of life, why does it seem to be so uncommon?

Why is the murmur confined to diastole although infants with persistent ductus arteriosus more commonly have either a systolic murmur or a continuous murmur

These four infants were part of a larger study of 73 early clamped and 127 late clamped healthy infants of normal birth weight who were serially examined during the first week of life. Although none of the late clamped infants had an isolated diastolic murmur the majority were examined less frequently than the early clamped infants on the first day of life Thus it cannot be definitely stated that they did not have such a murmur

It seems likely that the reason why an isolated diastolic murmur in the newborn infant has only been briefly mentioned by Burnard [6] who did not take into account the time of clamping of the cord is probably that the murmur is transient, variable and often difficult to record Thus phonocardiographic studies performed in a routine manner without auscultation might easily fail to record it.

The aortopulmonary pressure gradient is closely related to murmur production in patent ductus and certain conditions must prevail for this murmur to appear But in the presence of equivalent systolic pressures and lower pulmonary diastolic than systemic diastolic pressures a situation which is known to occur left to-right flow through the ductus should be expected to occur only in diastole. However until additional studies of infants with isolated diastolic murmurs are available interpretation must remain speculative.

Summary

This is the first detailed report of a transient diastolic murmur in the pulmonic area in healthy newborn infants. All four infants had immediate clamping of the umbilical cord and were from 2 to 4 hours of age when it was heard. Possible causes of this murmur are discussed.

Thanks are due to Professor John Lind who read the manuscript and gave valuable advice

REFERENCES

1 Lyon, R. A Rauh, L. W and Stirling, J W Heart murmurs in newborn infants, J Pediat. 16:310, 1940.
2 Hallidie-Smith K. A Some auscultatory and phonocardiographic findings observed in early infancy Brit M J 1 756 (March 2) 1960
3. Craige E., and Harned, H. S., Jr Phonocardiographic and electrocardiographic studies in normal newborn infants, Am. Heart J 65:180, 1963
4 Braudo, M and Rowe, R. D Auscultation of the heart—early neonatal period, Am. J Dis Child. 101:67 1961
5 Arcilla, R. A and Lind, J Serial phonocardiography during the neonatal period. A comparative study on infants born with early and late clamping of the cord, Ztschr Kinderh 93:354 1965
6. Burnard, F D A murmur from the ductus arteriosus in the healthy newborn baby Brit. M. J 1:806, 1958.
7 Arcilla, R. A Oh, W Lind, J and Gessner I H Pulmonary arterial pressures of newborn

infant born with early and lat clamping of the cord, Acta paediat. scandinav 55:305 1966
8. Emmanouilides, G. C., Moss, A. J Duffie E. R J and Adams, F H. P lmonary arteri l pressure changes i h ma newborn infant from birth t three days of age, J Pediat 65:327 1964
9 W lsh, S Z Early versus late clamping of the cord comparative study of the ECG in the neonatal period, Biol Neonat (In press)
10. Dawes, G S Mott, J C. and Widdicombe, J G. The cardiac murmur from the pat t ductu arteriosus i newborn lamb, J Physiol. 128:344 1955
11 Emmanouilides, G C., Moss, A. J and Adams, F H The electrocardiogram in ormal new born infants correlation with hemodynamic observations, J Pediat. 6 :578, 1965

Limitations of indicator dilution methods in estimation of cardiac output in chronic lung disease

A. Oriol, M.D.
N. Anthonisen, M.D.
M. McGregor, M.D., M.R.C.P., F.R.C.P. (C)
Montreal, Canada

The commonest method of measuring cardiac output by dye dilution techniques involves the rapid injection of a bolus of dye into the right atrium (RA) or superior vena cava (SVC) while the time-concentration curve is observed at a systemic arterial site. It is usual to exclude the effect of recirculated indicator by extrapolating to the baseline that portion of the downslope which appears to fall exponentially, as suggested by Hamilton and associates. Sekelj and Oriol[2] have previously shown that this technique may lead to considerable error in shock, when increased dispersion of indicator causes prolongation of transit times as the dye passes from injection to sample site in its first circuit. The primary time-concentration curve is thus prolonged and recirculation of some of the dye particles which first passed the sample site may take place undetected throughout most or all of the decay of the primary curve.

There is, however, another potential source of error which is inherent in the Hamilton technique of excluding recirculation. The assumption that the decay of the primary curve can be described by an exponential function would be true if the right and left heart were complete mixing chambers and if the transit times through all portions of the pulmonary vascular bed were identical. The good agreement between simultaneous estimates of cardiac output by dye and other techniques in the normal subject suggests that these conditions are reasonably well met. However, during studies involving intravenous injection of radioactive xenon, we have observed that in certain forms of chronic respiratory disease the transit times through different portions of the lung may differ very significantly. It was the object of the present study to investigate the extent of unevenness of perfusion in patients with chronic respiratory disease and to observe the influence this might have on the validity of the indicator dilution method of measuring cardiac output.

Dow[3] has previously shown that the area of the dye curve bears a constant relationship to its forward characteristics as reflected by appearance time, build up time, and peak concentration. We have shown elsewhere that cardiac output can be measured with reasonable accuracy in

From the Joint Cardiorespiratory Service of the Royal Victoria Hospital and the Montreal Children's Hospital and the McGill University Clinic, Montreal, Canada.
This work was supported in part by a grant from the John A. Hartford Foundation Inc. of the United States of America and Grant No. MT-12 from the Medical Research Council of Canada.
Received for publication June 3, 1967.
Address: Department of Cardiology, Royal Victoria Hospital, Montreal 2, Canada.

normal subjects by application of Dow's formula and that contamination of the downslope of the dye curve should be suspected when there is discrepancy between values derived from Dow's method and the technique of Hamilton. For this reason in a series of patients with respiratory disease we compared the cardiac output values obtained by measuring dye curve area by these two methods. Shortly thereafter, the flow through different areas of the lungs was studied with the use of injections of xenon [13] and regional counting techniques.

Method

This report involves data collected from 58 patients with chronic lung disease who were being studied for purposes unrelated to this communication. Diagnostic groups were as follows: emphysema, 30; bronchitis, 13; asthma in remission, 10; pneumonectomy for localized lung disease, 4; and one virtually normal subject with localized healed tuberculosis. The diagnosis was based on radiological and clinical examination, measurement of lung volume with its subdivisions, and estimates of intrapulmonary mixing, maximal midexpiratory flow rate, and carbon monoxide-diffusing capacity, all measured by techniques which have been described elsewhere.[4] Arterial oxygen and carbon dioxide content had been measured on one or more occasions in most patients.

When the diagnostic category had been established, each patient was studied as follows. Following placement of a transvenous catheter under fluoroscopic control into the axillary vein or S.V.C., patients were carefully positioned in the supine position over a rack containing 6 to 12 collimated scintillation detectors arranged so as to count over the whole posterior surface of the lung as described elsewhere. At the end of a quiet inspiration the subjects stopped breathing and a dose of 1.5 to 2.0 mc. of xenon [13] dissolved in 5 ml. of saline was flushed into the right heart with a further 20 ml. of normal saline, while the count rate at each counter field was recorded on magnetic tape. Shortly thereafter, dye dilution curves were performed by flushing approximately 2.5 mg. of indocyanine green dye or 40 mg. Coomassie blue dye into the right heart with 8 ml. normal saline. The time-concentration curves of the blue and green dyes were recorded by a calibrated ear oximetric method[6] or by withdrawing blood from the radial artery at a constant rate through a slightly modified whole blood cuvette oximeter.[5] After correction of the cuvette curves for the distortion introduced by the sampling system,[1] the areas of all curves were measured by application of Dow's formula in the manner previously described.[4] Thereafter, all curves were replotted on semilogarithmic paper and the area determined after the downslope which best fitted the experimental points had been extrapolated to baseline.

The output of each counter was played back through a ratemeter and recorded on a Sanborn polygraph. During its transit through the capillary bed somewhat more than 95 per cent of the xenon passed into the alveolus where it remained until eliminated by resumption of respiration.[7] Thus the rate of increase of counts over each area of lung represents the first integral of the time-concentration curve of the xenon in solution immediately prior to its release into the air spaces. By graphic differentiation of these curves at 1 second intervals, the shape of the indicator dilution curve in each portion of the lung could be estimated.

Results

In each of the 58 patients, two to five dye dilution curves were obtained, and the area of the 175 resultant curves was measured by both the Dow and Hamilton techniques. In each subject comparison was then made of the average value for cardiac output as estimated by each technique. The relationships between these values are shown in Fig. 1. In nine of the 30 emphysematous patients, values derived by the Hamilton method were lower by more than 15 per cent while there was agreement within these limits in all the other patients studied, with the exception of two asthmatic patients. It has been shown elsewhere that in normal subjects these two methods may be expected to agree within 15 per cent, and absence of agreement in the nine emphysematous patients suggests that one or both methods

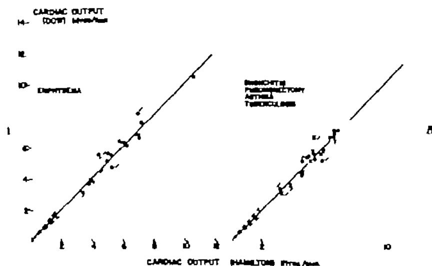


Fig. 1. Comparison of cardiac output estimations by the Dow (*A*) and Hamilton (*B*) techniques in patients with chronic respiratory disease. Lines indicate identity ± 15 per cent.

were in error. As indicated above, a likely source of error is in the existence of uneven perfusion of the lungs with resultant differences in transit times in different zones.

The xenon time-concentration curves recorded over six representative counter fields in a patient with healed apical tuberculosis are shown with their first derivatives, in Fig. 2. Appearance time and peak concentration time in each counter field are closely comparable. Cardiac output measured by the Dow and Hamilton techniques was 6.76 and 6.97 L. per minute respectively, a difference of 3 per cent. In this patient all lung function tests were within the normal range and the only evidence of disease was a small radiographic lung shadow. The close similarity of transit times in each lung zone is typical of all the patients reflected in Fig. 1,*B* (i.e., bronchitis, pneumonectomy, asthma). The average difference between the shortest and longest peak concentration time in the regional xenon curves in any one patient in this group was 1.2 seconds and the greatest difference observed was only 1.6 seconds.

By contrast, the regional xenon curves in patients with moderately severe emphysema exhibited a wide range of appearance times and peak concentration times. An example is shown in Fig. 3. Cardiac output values based on Dow and Hamilton techniques in this patient were 5.86 and 4.53 L. per minute, respectively, a difference of 29 per cent. The wide variation in regional transit times in different lung zones was typical of those patients with emphysema in whom there was discrepancy between Dow and Hamilton estimates of cardiac output. In nine instances in which estimates of cardiac output differed by more than 15 per cent (Fig. 1,*A*) the average difference between the shortest and longest peak concentration time in any one patient was 5.3 seconds (range 3.3 to 8.8 seconds). It should be noted that these values reflect differences in transit time from pulmonary artery to capillary and that differences are probably further increased during passage of indicator from capillary to left atrium.

Discussion

The occurrence of patchy reduction of arterial size is a well recognized radiologic feature of emphysema and it has also been recognized that flow to emphysematous areas of lung may be reduced. If the reduction of flow paralleled the reduction in arterial volume with consequent preservation of flow-to-volume ratios throughout the pulmonary arterial bed the form of the dye curve would not be distorted. In nine of these emphysematous patients, however, this was not the case.

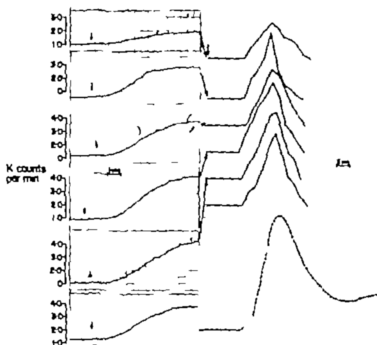


Fig. 2 Studies of regional lung blood flow in a normal subject. Original records (left) of the count rate over representative areas of lung following an injection into the axillary vein of 1.5 mc. of Xe[133]. The arrow indicates the appearance of xenon in each counter field. On the right, is the first derivative of each of these curves, obtained by graphic methods at 1 second intervals. Below (interrupted line) the dye dilution curve is shown for comparison.

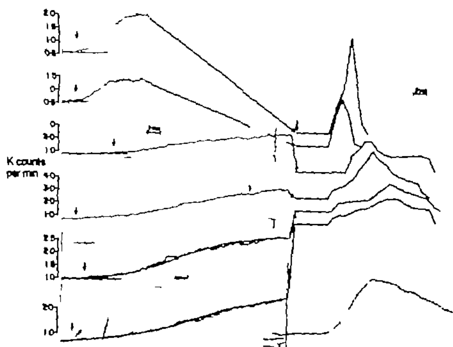


Fig. 3 Studies of regional pulmonary blood flow in a patient with severe emphysema. It can be seen that the appearance times recorded in each counter field are grossly discrepant. The dye curve is shown below for comparison (interrupted line).



Fig 4 Semilogarithmic replot of the dy dilution curves shown in Figs. 2 and 3. I the normal curve on the left there is an exponential-like decay hich is 5 seconds in duration. *R* marks the probable onset of recirculation. Hamilton nd Dow estimates of cardiac output agree closely I the abnormal curv on the right an rbitrary exponential slope has been forced through the experimental poi ts. *K* marks the onset of this slope hile *R* and *R* indicate estimates of the time of onset of recirculation

The nhomogeniety of flow volume ratios in different lung zones observed in these cases could cause discrepancy between Dow and Ham lton estimates of cardiac output in several ways. The constant relationship observed by Dow between the forward characteristics of the normal dye curve and its total area is most unlikely to exist when inhomogeneous pulmonary perfusion results in such gross distortion of the arterial dye dilut on curve as is seen in Fig 3 Thus, th Dow formula will not predict curve rea w th accuracy in such c ses.

At the same time it is also most unlikely that estimates based on Hamilton s method of measuring curve area will be accurate This technique will be in error for two reasons. (1) Any resemblance of any part of the downslope to a single exponential function in such cases must be purely coincidental and extrapolation of any por t on of downslope will not validly represent the manner in which the primary curve would have decayed in the bsence of re circulation. (2) Although lung disease may cause prolongation of the dye curve there is no reason to nticipate that systemic recirculation will be abnormal in such patients. Thus, some of the first indicator to enter the systemic arterial bed will likely recirculate throughout most or all of the downslope of the primary curve when this is greatly prolonged This is illustrated in Fig 4 which shows the same curves illustrated in Figs. 2 and 3 redrawn on a semilogarithmic scale In the normal curve on the left there is a fairly long exponential-like downslope wh ch decays to one third peak concentration before obvious recirculation This appears to commence at R, approximately 12 seconds from the time of appearance The replot of the emphysematous curve (Fig 4 right) is more irregular The decay is approximately linear for a period of 9 seconds, that is from K to the point of apparent recirculation also at one third peak concentration. The velocity of recirculation n the systemic circulation is unknown but there is no apparent reason why t should be retarded If the onset of recirculation is assumed to be 1 seconds from appearance t me (R) as in the normal curve on the left it is clear that the whole downslope is contaminated by recirculation and even if recirculation commences as late as 16 seconds

must influence the rate of decay of the dye curve to a significant extent.

Because the dye dilution technique is simple and has such wide acceptance as a method of measuring cardiac output in the normal circulation there is frequent temptation to employ it in situations in which it is not applicable. This study indicates that the inhomogeneity of pulmonary flow which may be found in chronic emphysema is one of these situations. In shock the dye curve area can still be estimated by application of Dow's formula even when the downslope is contaminated by recirculation.[2] The distortion of the primary curve observed in these cases of emphysema, however, makes it most unlikely that accurate values can be obtained even by these means.

Summary

In 58 patients with chronic lung disease the validity of Hamilton's method of measuring cardiac output was tested by making comparison with values based on Dow's formula. In patients with bronchitis or asthma and those who had had pneumonectomy for localized lung disease there was good agreement. In nine of 30 patients with emphysema, however, values based on the Hamilton technique were lower by more than 15 per cent.

In these patients a bolus of xenon [133] was injected intravenously while its arrival in 6 to 12 areas of the lung was monitored by scintillation detectors and the first derivative of the resultant time-concentration curve was obtained by graphic methods. In those with bronchitis, asthma, and pneumonectomy in which Dow and Hamilton values for cardiac output were similar, both the time of arrival and the time of peak concentration of xenon were closely comparable in each lung zone. In most emphysematous patients, however, arrival time and peak concentration time differed widely in different lung zones. The downslope of the first circulation, although apparently an exponential function, cannot validly be extrapolated. Furthermore, due to prolongation of the primary curve the downslope must become contaminated by recirculation. The use of Hamilton's method in the analysis of dye dilution curves in such patients is thus likely to be erroneous.

The authors wish to express their great indebtedness to Miss J. Doman and Mr. W. R. D. Ross for invaluable assistance in the performance of dye and xenon techniques, respectively.

REFERENCES

1. Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: Studies on the circulation. I. Injection method: Physical and mathematical considerations, Am. J. Physiol. 89:322, 1929.
2. Sekelj, P., and Oriol, A.: Dye curve errors in shock, Fed. Proc. 26:332, 1967.
3. Dow, P.: Dimensional relationships in dye-dilution curves from humans and dogs, with an empirical formula for certain troublesome curves, J. Appl. Physiol. 7:399, 1955.
4. Sekelj, P., Tait, C. R., and Nathanson, M. M.: Studies on dye dilution curves using a digital computer, I.E.E.E. Tr. Biomed. Eng. BME 13:32, 1966.
5. Oriol, A.: Determination of cardiac output, using Dow's formula, J. Appl. Physiol. 22:588, 1967.
6. Bates, D. V., and Christie, R. V.: Respiratory function in disease. An introduction to the integrated study of the lung, Philadelphia and London, 1964, W. B. Saunders Company.
7. Ball, W. C., Jr., Stewart, P. B., Newsham, L. G. S., and Bates, D. V.: Regional pulmonary function studies with xenon[133], J. Clin. Invest. 41:519, 1962.
8. Sekelj, P., and McGregor, M.: Estimation of cardiac output in man using an ear oximeter and Coomassie blue dye, IRE Tr. Biomed. Electronics 8:127, 1961.
9. Sekelj, P., Oriol, A., Anderson, N. M., Morch, J., and McGregor, M.: Measurement of indocyanine green dye with a cuvette oximeter, J. Appl. Physiol. 23:114, 1967.
10. Sherman, W. R., and Jose, A. D.: Distortion of indicator dilution curves by sampling systems, J. Appl. Physiol. 15:177, 1960.

Congenital aneurysm of the sinus of Valsalva associated with ventricular septal defect

Anatomical aspects

*Shigeru Sakakibara M D**
*Souji Konno M D***
Tokyo Japan

The sinuses of Valsalva are located at the commencement of the aorta. Pocketlike spaces constructed from the three aortic cusps and the aortic wall which is somewhat dilated at this level form three bulges which are anatomically designated as the aortic sinuses of Valsalva (Fig. 1 A [1])

Sometimes the sinuses of Valsalva have a congenital weakness of the tissue structure. When a ventricular septal defect (VSD) exist just below such a weakened structure the sinuses come into communication with the aortic valves. The bulging of these valves and sinuses into the VSD causes aortic insufficiency. Because of the high pressure in the aorta a diverticular aneurysm ma thus arise in the weak tissues of the sinuses. This condition is called "congenital aneurysm of the sinuses of Valsalva" (Fig. 1 A 1) The aneurysm may be a result onl of the anatomicohemodynamic disorder created by VSD or it may result from this disorder combined with a weakness of the sinus.

Because of the variety of signs and symptoms presented by the patient during the different stages in its development it has been neither sufficiently understood nor accurately classified For example, a very early lesion where the aneurysm is too small to be detected has been designated by some authors as a subtype of VSD associated with aortic insufficiency On the other hand a late lesion with a full grown aneurysm has been coded as aneurysm of the sinuses of Valsalva, associated with interventricular communication and aortic insufficiency [2] Other lesions, in varying transitory stages, have been interpreted either as aneurysms of the sinuses of Valsalva with interventricular septal defect or as interventricular septal defect with aortic insufficiency Approximately 150 such cases have been reported in the literature but most reports deal with only one or a few cases. For this reason coding into various types has been nearly impossible, but it is obvious that treatment and diagnosis urgently need a fundamental basis for classification of the various stages. In this paper we attempt to establish such a basis We analyze 55 operative and 15 autopsy cases in detail compare them with cases reported by others, and code analogous types in an attempt to bring some order into the classification

Received for publication June 2, 1962
*Director the Heart Institute of Japan, Professor of Cardiac Surgery
**Chief Staff of the Heart Institute of Japan Head of Cardiac Catheterization Room.

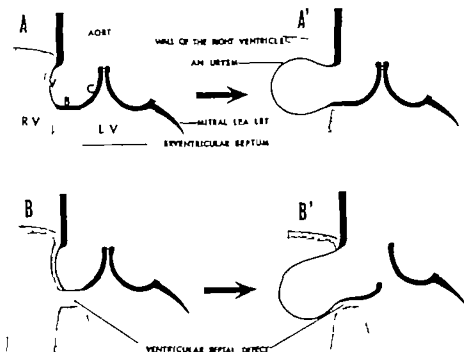


Fig. 1 Schematic illustration of the development of congenital neurysm of the sinuses of Valsalva. 1 A Type I B–B' Type I VSD N t the anatomical relationship of the portion of weakness in the si ses of V lsalv the entric lar septal defect existing just below it nd the ortic al es. RV Right entricle LV left entricle See text for further discussion.

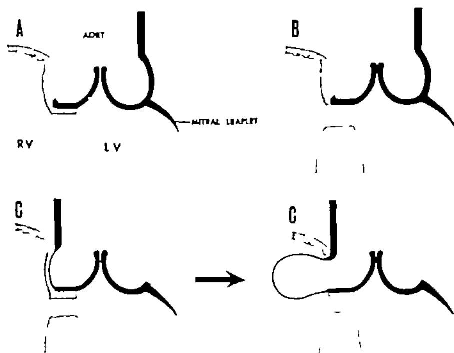


Fig. 2 Schem illust ting the relationship of the sinuses of Valsalva aortic lves nd ventricular septal defect. A seen from A and B the development of aneurysm and sagging of the aortic alve do not occur when the sinuses of Valsalva ha normal tructural strength even if entricular septal defect exists just below the aortic lve. When the part of weakness i the sinuses of Valsalv nd the entricular septal defect are somewhat distanced I C growi g aneurysm does not cause the sagging of the aortic valve (C')

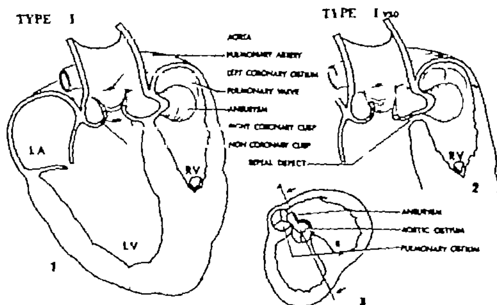


Fig 3 Section 2 shows the schema of the anatomical situation of the aneurysm of the sinuses of Valsalva in Type I VSD Note the anatomical relationship to the pulmonary valves. Section 3 is horizontal section of the heart seen from above Sections 1 and 2 are the schema of the heart cut longitudinally at the line of A-A and viewed from the direction of the arrow

Discussion

Strictly speaking an aneurysm rarely arises only from the portion of the aorta in which the sinuses of Valsalva are located. It frequently overrides into those areas designated as *B* and *C* of Fig 1 A When a VSD presents just below the aortic valve portions *B* C and I (Fig 1 A) fuse together and make a common protrusion into the septal defect. In such instances the free margin of the aortic cusp is retracted and aortic insufficiency results (Fig 1 *B-B'*)

The first report dealing with this syndrome was published by Hart in 1905 in it he discussed the development of the syndrome on the basis of one of his own cases. Similar cases have occasionally been reported since that time since the appearance of an article by Scott in 1958 the designation VSD with aortic insufficiency has frequently been used However definite classification of this syndrome has not been settled yet

It has been assumed that the syndrome is caused when a VSD presents just below the aortic valve which loses its support



Fig 4 The heart of typical Stage III of Type I VSD viewed from the side of the right ventricle The probe *A* is introduced from the aorta the ruptured portion of the sinuses of Valsalva The probe *B* is passed from the left ventricle to the right ventricle through the ventricular septal defect *LP* Left cusp of the pulmonary valve *P* papillary muscle of the conus *T* tricuspid valve

and falls into the septal defect However it is very important to establish carefully whether in these cases the VSD (1) is located in the membranous portion of the ventricular septum or (2) is localized in the infundibulum of the pulmonary artery

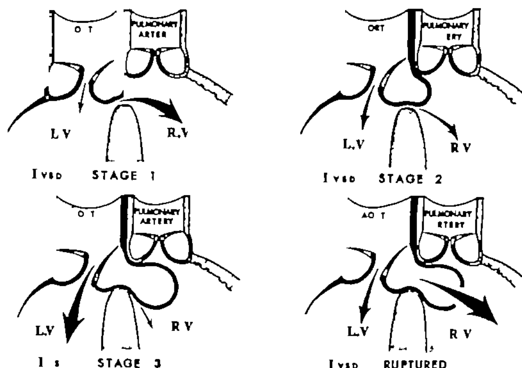


Fig. 5. Schematic drawing of growing process of aneurysm of the sinus of Valsalva of Type I VSD. *LV*, Left ventricle; *RV*, right ventricle. Arrows represent aortic regurgitation and interventricular shunt.

In the first condition aneurysm of the sinus of Valsalva is extremely unusual but in the second it is common. Despite a relatively large defect in nine autopsy cases in our series, in which all subjects were over 60 years of age, the lesion remained as shown in Fig. 2,*B*. Aortic insufficiency seems to arise only if the VSD exists just below the aortic valve and if, at the same time, the tissues of the sinuses of Valsalva are weak (Fig. 1, *B*, *B*). Fig. 1,*B* illustrates a case in which the sinuses of Valsalva and the aortic valve produce a common bulge and fall into the septal defect. Here the congenital weakness of the sinuses of Valsalva is extremely important both histologically and anatomically.

Because we believe that this syndrome should be understood as a variant of the condition called "aneurysm of the sinuses of Valsalva," we have classified congenital aneurysms into four types (I to IV) depending on the location of the lesion. When a VSD is associated, the types are coded as I VSD, II VSD, III VSD, and IV VSD.

Classification

Type I VSD. In this type a VSD is present immediately below the commissure of the left and right semilunar cusps of the pulmonary valves. The sinuses of Valsalva occupy the left third of the right coronary sinus which, together with the aortic valve, forms an aneurysm (Fig. 3, *2*).* The aneurysm bulges, gradually falls into the VSD, extends to the outflow tract of the right ventricle, and finally ruptures, forming an aortic right ventricular fistula. The result is heart failure and death (Fig. 4). To facilitate further discussion, development of the aneurysm has been divided into three stages (Fig. 5). Although it cannot be established definitely that Type I VSD develops from Stages 1 to 3, leading to rupture of the aneurysm and death of the patient, the age distribution

*This is the type frequently found in Japan.[14] It constitutes 95 per cent of the congenital aneurysms of the sinuses of Valsalva reported in the country. Because of the difficulties involved in surgical correction and the problems presented if no operation is instituted, the present paper is largely devoted to consideration of this type.

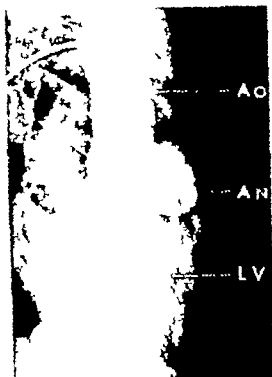


Fig 6 Retrograde aortograph in lateral projection of the patient with Type I VSD aneurysm in Stage III A aorta A aneurysm LV left entricle.

of the patients in the respective stages in our series seems to support this theory

STAGE 1 Operative and autopsy specimens reveal that the aneurysm when viewed from the side of the right ventricle does not bulge into the right ventricle at this stage although it nearly covers the VSD (Fig 5 1) A lateral aortograph gives no evidence of the bulging of the sinuses. The symptomatology is dominated rather by aortic insufficiency resulting from the sagging of the right coronary cusp There is slight-to-moderate regurgitation of the cont ast substance into the left ventricle, and some of the substance passes into the right ventricle through the VSD thus the ight ventricle and the pulmonary artery are revealed in the film (Fig 7 1)

STAGE 2 The operative and autopsy specimens, again v ewed f om the side of the right ventricle reveal a hemispheric aneurysm protruding into the right ventricle through a VSD The aneurysm completely obstructs the VSD at the diastolic

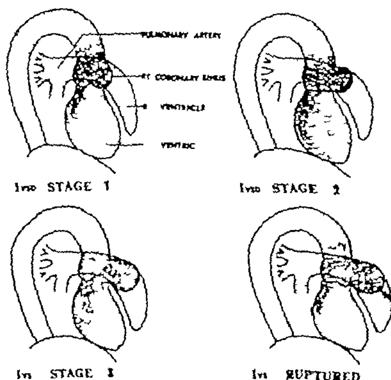


Fig 7 Schematic d of the etrograde aortography in the lateral projection of Type I VSD aneurysm in arious tages

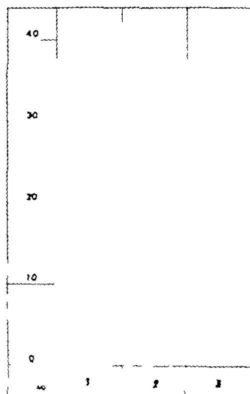


Fig. 8. Ordinates, age of the subjects; abscissae, stages of the aneurysm. (Data of 55 operation and 11 autopsy cases in our series and 45 cases reported by other authors.)

phase (Fig. 5, 2). Rupture of the aneurysm is rare at this stage, but it can occur if inflammation is present. Lateral angiocardiography shows the aneurysm clearly. In this stage it bulges to less than half of the diameter of the aorta, and aortic regurgitation is moderate. Filling of the right side of the heart is not seen at this stage because the aneurysm has closed the VSD (Fig. 7, 2).

STAGE 3. When this stage has been reached, the aneurysm (viewed again from the side of the right ventricle) appears almost spherical. The tip is larger than the base, making retraction to the side of the left ventricle difficult. The VSD is completely occluded throughout the diastolic and systolic phases. The portion of the sinuses with minor resistance frequently bulges to a cumulous shape and may become the site of future rupture (see the lower two sections of Fig. 5). Lateral angiocardiography now reveals the silhouette of a large saccular aneurysm, and the degree of bulging frequently exceeds half of the aortic diameter. When rupture of the aneurysm impends, the portion with least resistance is a small protrusion about the size of a pea (Fig. 6). Regurgitation from the aorta to the left ventricle is extensive, but the VSD remains obstructed so that the right side of the heart cannot be seen in the film. However, when the aneurysm finally ruptures, a hemodynamic change results, making the right ventricle more clearly demonstrable than the left (see the lower right section of Fig. 7).

Twelve of our cases were patients with typical VSD who developed aortic insufficiency during the follow-up period in the Pediatrics Department of this institute. Holosystolic murmur with maximum audibility at the left third interspace and palpable thrill, left axis deviation, and left preponderance in electrocardiography pointed to a VSD, which was confirmed by cardiac catheterization. A blowing diastolic murmur radiating from the third interspace medially was audible caudally for some time afterwards. Although the murmur was not always present at first, approximately three months later it was constantly audible and had developed into a typical to-and-fro murmur. The onset of this diastolic murmur occurs in most patients between the ages of three and seven. Four of our patients (classified as Stage 1) were operated on within one year after onset of this murmur, and two other patients (Stage 2) were operated on two and three years after onset, respectively. See Fig. 8, in which the age of the subjects is plotted against the stage of the aneurysm.

Type II VSD. In this type the VSD rests on the crista supraventricularis; it is not in contact with the tricuspid or pulmonary artery valves. The corresponding sinuses of Valsalva (that is, the central portion of the right coronary sinus and the aortic cusp) form an aneurysm and fall into the VSD (Fig. 9, 2). This is a rare type, to which only four subjects in our series belonged. It appears that this type may develop through stages similar to Type I VSD,[17] but detailed analysis is at present impossible.

Although the VSD is usually found just below the sinuses of Valsalva, a firm tissue

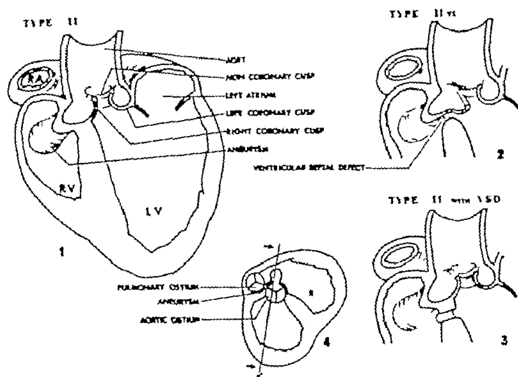


Fig. 9. Section 2 shows the schema of the anatomical situation of the aneurysm of the sinuses of Valsalva, Type II VSD. Section 4 is horizontal section of the heart seen from above. Sections 1, 2 and 3 are the schema of the heart cut longitudinally at the line of *B–B'* and viewed from the direction of the arrow.

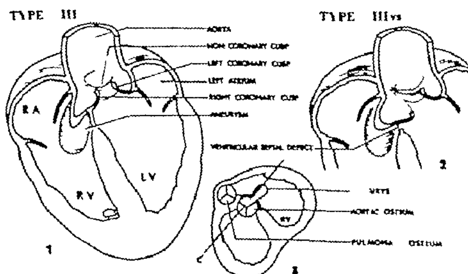


Fig. 10. Section 2 shows the schema of the anatomical situation of the aneurysm of the sinuses of Valsalva in Type III VSD. Note anatomical relationship to the tricuspid valve. Sections 1 and 2 are the schema of the heart cut longitudinally at the line of *C–C'* and viewed from the direction of the arrow.

about 2 to 3 mm in width was found between them in three of our subjects. Similar cases have been described by other workers [14] (Fig 9 *3* and Fig 2 *C'*) Surgical correction of this situation is easy because the aortic valves are naturally intact

While the VSD and the aneurysm of the sinuses are close to each other in these instances, they are not interdependent as in Types I VSD and II VSD They should therefore be regarded as cases of coincidental association of two independent malformations and should be classified as Type II *with* VSD rather than as Type II VSD (Fig 2 *C–C'*)

Type III VSD The size of the aneurysm in this type is not as large as it is in Type I VSD The VSD lies just below the crista supraventricularis and the corresponding sinus of Valsalva The right third of the right coronary sinus and the aortic valve develop to form an aneurysm and fall into the VSD (Fig 10 *2*) We have only four such cases, but a number of similar examples have been reported in the literature of other countries. [20-22]

Type IV VSD The VSD rests on the pars membranacea in this type The corresponding sinus of Valsalva (the right third of the noncoronary sinus and the aortic valve) produces an aneurysm and falls into the VSD This type of lesion appears to be rare[23,24] descriptions of cases previously reported are not full and we have no similar cases in our own collection For this reason a detailed study of Type IV VSD cannot be done at the present time.

Summary

On the basis of 55 operative and 15 autopsied specimens, the relation of VSD aneurysm of the sinuses of Valsalva, and prolapsing aortic insufficiency has been discussed Four types were grouped analogously to our previous classification of the congenital aneurysm of the sinus of Valsalva. With this classification as a basis, anatomical and angiocardiographic findings of the disease were compared and analyzed

REFERENCES

1 Scott, R. C., McGuire, J Kaplan, S., Fowler N O Green R. S Gordon, L. Z., Shabetai, R. and Davolos, D D The syndrome of ventricular septal defect with aortic insufficiency Am J Cardiol. 2:530, 1958.
2. Hart, K.: Über das Aneurysma des rechten Sinus Valsalvae der Aorta und seine Beziehungen zum oberen Ventrikelseptum Virchow Arch f pathol. Anat. u. Physiol 182 167 1905
3. Sakakibara, S and Konno, S.: Congenital aneurysm of the sinus of Valsalva Anatomy and classification AM. HEART J 63:405 1962.
4 Sakakibara S and Konno, S. Congenital aneurysm of the sinus of Valsalva A clinical study AM. HEART J 63 708, 1962.
5 McGoon, D C Edwards, J E., and Kirklin, J W Surgical treatment of ruptured aneurysm of aortic sinus, Ann. Surg 147:387 1958.
6 Giallorreto, O P and Loiselle, G. Aneurysm of aortic sinus of Valsalva associated with high ventricular septal defect Am. J Cardiol. 11:537 1963
7 Gerbode, F Osborn, J J Johnston J B and Kerth W J: Ruptured aneurysms of the aortic sinus of Valsalva Am. J Surg 102:268, 1961
8 Bloffman, B., and Elder J C.: Cardioaortic fistula Temporary circulatory occlusion as an aid in diagnosis, Circulation 16 77 1957
9 Lin T K., Crockett J E. and Dimond, E. G. Ruptured congenital aneurysm of the sinus of Valsalva, AM. HEART J 51:445 1956.
10. Burchell H B and Edwards, J E. Aortic sinus aneurysm with communications into right ventricle and associated ventricular septal defect, Proc. Staff Meet. Mayo Clin. 26:336, 1951
11 Sakakibara S and Konno, S Successful surgical repair of aneurysm of the sinus of Valsalva (In Japanese) Operation 14 725 1960.
12 Sugie, S., et al. Aneurysm of sinus of Valsalva ruptured into right ventricle case report (In Japanese) Respiration & Circulation 3:270, 1955
13. Shibuya, M et al. Ruptured congenital aneurysm of right sinus of Valsalva diagnosed during life (In Japanese) Respiration & Circulation 7:509 1959
14 Oguro, C. et al. Congenital aneurysm of sinus of Valsalva ruptured into right ventricle (In Japanese) Respiration & Circulation 5:443, 1957
15 Sakakibara, S and Konno, S.: Congenital aneurysm of the sinus of Valsalva, Am. J Cardiol. 12 100, 1963
16. Taguchi, K et al. Treatment of aneurysm of sinus of Valsalva complicated with aortic bicuspid valve (In Japanese) Jap. J Thoracic Surg 18:847 1965
17 Fabricius, T J and Davidsen, H C Aneurysm of the aortic sinus of Valsalva Ruptured to the right ventricle and successful surgical repair Acta chir scandinav Suppl 283 129 1961
18. Winchell P., and Bashour F Ventricular septal defect with aortic incompetence simulating patent ductus arteriosus, Am. J Med. 20:361 1956.
19 Hurst, W D and Schemm, F R: High ventricular septal defect with slight dextroposition of the aorta, which presented the clinical fea

tures of patent ductus arteriosus, AM. HEART J 36:144 1848
20. White, W. H. A case of patent ventricular septum, together with an aneurysm of the base of the aorta opening into the right ventricle T. P th. Soc. London 43:31, 1892.
21. Ash, R. and Murphy L. High ventricular septal defect and light dextroposition of the aorta associated with deformed aortic valve simulating patent ductus arteriosus, J. Pediat. 37:249 1950
22. Taussig H B., and Semans, J. A. Severe aortic insufficiency in association with congenital malformation of the heart of the Eisenmenger type, Bull. Johns Hopkins Hosp. 66 156, 1940.
23. Menache S. A. and Dotter C. Surgical correction of aortic insufficiency associated with ventricular septal defect, Surg. G nec & Obst 111 71 1960
24. Ellis, F. H. Ongley P. A. and Kirklin, J. W. Ventricular septal defect with aortic valvular incompetence. Surgical considerations. Circulation 27 789 1963
25. Magidson, O. and Kay J. H. Ruptured aortic sinus aneurysms. Clinical and surgical aspects of seven cases, AM. HEART J 65:597 1963
26. Claypool, J. G. Ruth, Wm., and Lin, T. K. Ventricular septal defect with aortic incompetence simulating patent ductus arteriosus, AM. HEART J 84 788 1951
27. Allen, A. C. A case of bacterial endocarditis illustrating the mechanism of localization and the nature of vegetations, AM. HEART J 21:667 1941
28. Denton, C. and Pappas, E. G. Ventricular septal defect and aortic insufficiency. Report of three cases, AM. HEART J 2:554 1958.
29. Kieffer S. A. Congenital aneurysms of the aortic sinuses with cardioaortic fistula, Dis. Chest 38 79 1960.
30. Spencer F. C. Bahnson, H. T. and Neill, C. A. The treatment of aortic regurgitation associated with ventricular septal defect, J Thoracic Cardiovas Surg 43:222, 1962.
31. Besterman, E. M. M. Goldberg, M. J. and Sellors, T. H. Surgical repair of ruptured sinus of Valsalva, Brit. M. J. 5354:410 1963
32. Nadas, A. S., Thilenius, O. G. LaFarge C. G., and Hauck A. J. Ventricular septal defect with aortic regurgitation. Medical and pathological aspects, Circulation 29:862, 1964.
33. Halloran, K. H. Talner N. S. and Browne M. J. A study of ventricular septal defect associated with aortic insufficiency AM. HEART J 69:320 1965.
34. Asano, K. Washio, M. Shiozaki, K. Eguchi, S. Mitsuzawa, T. and Matsukura, T. Surgical treatment of the ruptured aneurysm of the aortic sinus (in Japanese) Jap. J. Thoracic Surg 20:520, 1967

Anatomic types of ventricular septal defect with aortic insufficiency

Diagnostic and surgical considerations

Richard Van Praagh, M.D.
J. Judson McNamara, M.D.
Boston, Mass.

Recent reports concerning ventricular septal defect (VSD) with aortic insufficiency (AI) have done much to clarify the clinical, hemodynamic, and surgical aspects of this serious problem. However, the pathologic anatomy remains incompletely understood in several important respects. A knowledge of conal (infundibular) anatomy, when applied to this problem, proved illuminating.

The purposes of this report are: (1) to present the principal pathologic findings in 11 postmortem cases, (2) to propose an anatomic classification of VSD with AI, (3) to attempt to clarify the pathogenesis of the AI in the several anatomic types, and (4) to consider the salient diagnostic and surgical implications of the anatomic findings.

Findings

Classification. Two main types emerged: (1) those with a subcristal VSD, i.e., defect beneath the crista supraventricularis (parietal band or conal septum), Type I, and (2) those with a subpulmonary VSD, i.e., defect beneath the pulmonary valve, Type II.

Subcristal VSD with AI (Type I) has two subtypes: those with an essentially normal subpulmonary conus, typically with no infundibular pulmonary stenosis (PS), Type Ia (Fig. 1), and those with some degree of underdevelopment of the subpulmonary infundibulum with deviation of the crista supraventricularis away from the tricuspid valve in an anterior, superior, and leftward direction and with hemodynamic evidence of pulmonary infundibular stenosis of mild to moderate degree, Type Ib (Fig. 1). Such deviation of the crista was similar to that seen in typical tetralogy of Fallot, except that in our cases of Type Ib it was milder in degree and the patients all were acyanotic.

The proposed anatomic classification of VSD with AI (Fig. 1) is similar to that of Nadas and associates,[4] except for the division of Type I into two subtypes.

SUBCRISTAL VSD WITH AI (TYPE IA). Case 2 is typical (Fig. 2 and Table I). From the right ventricular aspect (Fig. 2,a) the VSD is seen to be small and subcristal. The crista supraventricularis is not deviated away from the tricuspid valve. Consequently, there is no pulmonary infundibular stenosis and no pulmonary outflow tract gradient was found at cardiac catheterization. Right ventricular hypertrophy is minimal and the right ventricular pressure was only 35/0 mm. Hg with a small left-to-right shunt (Q_p/Q_s = 2.3/1).

From the left ventricular aspect (Fig.

From the Division of Cardiology and the Departments of Surgery and Pathology, Children's Hospital Medical Center and Harvard Medical School, Boston, Mass.
Supported by grants from the National Heart Institute of the National Institutes of Health.
Received for publication June 27, 1967.

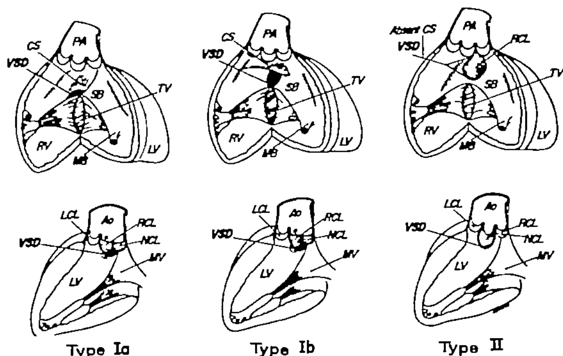


Fig. 1. Anatomic types of VSD ith AI. Subcristal ventricular septal defect (*VSD*) ith aortic sufficiency (*AI*) is T pe Ia. Subcristal VSD with AI and inf ndibular pulmonary stenosis is Type Ib. Subpulmonary VSD with AI is Type II. Classification is considered in the text. A aorta, *CS* conal septum or crista supraventricularis, *LCL*, left coronary leaflet, *LV* left entricle, *MB* moderator band, *MV* mitral alv, *NCL* noncoronary leaflet, *PA* pulmonary artery, *RCL*, righ coronary leaflet, *RV* right entricle, *SB* septal band, *TV* tricuspid alv e. The same abbreviations are used i all figures (art by Mary E. Mellow).

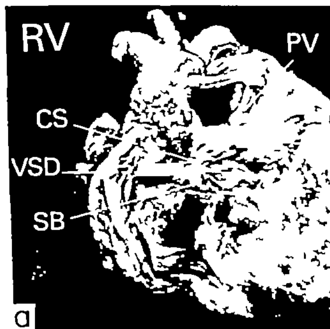


Fig. 2a. Subcristal V... ...th AI (Type Ia) ...se 2 (Table I). Aortic alv is elev ted in ... t expose small VSD. All heart specimens are described ... the text (photography by Frederick Clow.



Fig. 2,b For legend see under Fig. 2,a

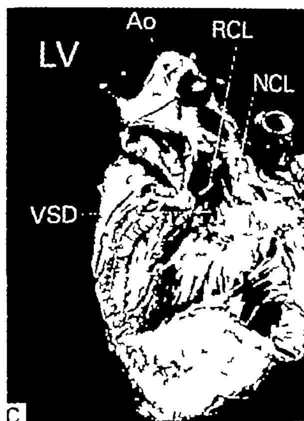


Fig. 2,c For legend see under Fig. 2,a

Table I Findings in 11 postmortem cases of VSD with AI

Type	Case No.	Sex	Age at death (yr.)	Pulmonary conus	VSD: Dimensions (cm.)	VSD: Size	Aortic valve: Lost commissure	Aortic valve: Bicuspid	Aortic valve: Prolapsed leaflet	Pulmonary gradient (mm. Hg)	Addenda
Ia	1	F	14 10/12	Normal	0 3 × 0 3	S	RC NC	+	RC NC	32	Prominent, high moderator band
	2	M	3 8/12	Normal	0 2 × 0 4	S	RC NC	+	RC NC	0	Single umbilical artery
	3	M	20 7/12	Normal	0 3 × 0 3	S	RC-LC	+	NC	0	Aneurysm of pars membranacea septi. History of SBE and cerebral infarct
Ib	4	M	4 7/12	Deviated CS	0 6 × 0 3	S	NC LC	0	NC, RC	40	Right aortic arch
	5	M	24 6/12	Deviated CS	2 3 × 0 9	M	RC NC	+	RC NC	9	
	6	M	7 11/12	Acyanotic TOF	1 3 × 1 0	M	RC-NC	+	RC NC	40	Bicuspid pulmonary valve
	7	F	15 5/12	Deviated CS	1 5 × 0 5	M	0	0	RC, C	13	RC leaflet herniates through VSD into RV
II	8	M	21 1/12	Absent CS	2 0 × 1 0	M	0	0	RC	34	History of SBE
	9	M	13 11/12	Absent CS	2 0 × 1 0	L	0	0	RC, NC	15	
	10	F	7 3/12	Cleft CS	1 0 × 0 4	S	0	0	RC	15	
	11	M	15 1/12	Absent CS	2 0 × 1 0	M	0	0	RC	50	History of SBE, Meckel's diverticulum, extensive LV infarction, subendocardial

Seven of the foregoing cases (1, 2, 3, 7, 8, 9 and 11) were reported previously by Nadas and associates

2,*b* and *c*) the smallness of the VSD is even better appreciated But the most striking finding is the regurgitant aortic valve The right coronary noncoronary commissure is rudimentary (Fig 2,*b*) This results in a bicuspid aortic valve with a combined right coronary noncoronary leaflet. This large, poorly supported combined aortic leaflet is prolapsed markedly downward. It may well have largely occluded the VSD during diastole. The thickening and rolling of the free margins of the aortic leaflets indicate severe AI which was documented by cineaortography and by widening of the pulse pressure (95 30 mm Hg in the ascending aorta)

An unusual example for this series, of subcristal VSD with AI (Type Ib) is shown in Fig 3 (case 3 Table I) The right ventricular anatomy appears normal (Fig 3,*a*) except for a small aneurysm of the pars membranacea septi in the center of which there is a very small defect. This is a purely membranous VSD it involves only the membranous portion of the inter ventricular septum The left to-right shunt was minimal (Q Q = 1 1 1 0) documented by cineangiocardiography as well as by oxygen data, and the right ventricular pressure was 32 7 to 12 mm. Hg hence the absence of demonstrable right ventricular hypertrophy and enlargement (Fig 3,*a*)

The smallness of the VSD is best appreciated from the left ventricular aspect (Fig 3,*b*) The aortic valve displays absence of the intercoronary (right coronary left coronary) commissure (Fig 3,*c*) Functionally this is a bicuspid aortic valve

This case illustrates that when an aortic commissure is defective prolapse does not necessarily involve the aortic leaflet with the defective commissure. The right and left coronary leaflets are deprived of their normal attachment to the aortic wall at the septal commissure but it is the normally attached noncoronary leaflet which is prolapsed resulting in aortic regurgitation The large combined coronary leaflet overlies the smaller prolapsed noncoronary leaflet Such malalignment of the leaflet margins appears to have prevented competent closure Both leaflets seem to have lacked the support afforded by normal cusp apposition in diastole However the absence of normal leaflet apposition appears to have been a secondary effect produced by absence of the intercoronary commissure resulting in a large overriding combined coronary leaflet and a small

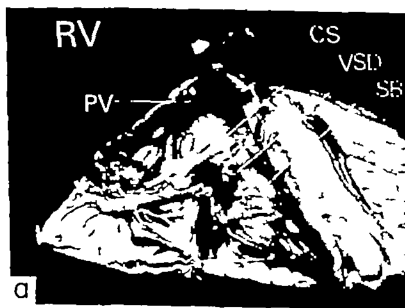


Fig 3,a Subcristal VSD b AI (Type I) case 3 (Table I). I bicuspid aortic valve is viewed from above and from the left (left superior oblique).

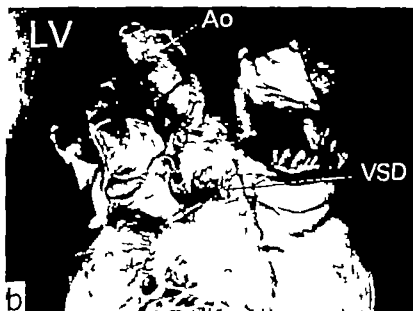


Fig. 3,b For legend, see under Fig. 3,a



Fig. 3,c For legend see under Fig. 3,a

underlying noncoronary leaflet thereby setting the stage for AI and progressive prolapse of the underlying noncoronary leaflet

The severity of the AI is indicated anatomically by the thickening and rolling of both leaflet margins (Fig. 3,c) and by the marked left ventricular hypertrophy and enlargement (Fig. 3,a and b). The pulse pressure was considerably widened (170/40 mm Hg brachial artery) and the left ventricular end diastolic pressure was elevated (170/20-28 mm Hg)

Thus, case 3 (Fig. 3) contrasts with the other two cases of Type Ia in the following respects (Table I) different commissure

defective prolapse of the aortic leaflet with normal commissures and VSD almost closed.

Table I indicates that all three cases of Type Ia have small VSD's. All have bicuspid aortic valves due to rudimentary development of one aortic commissure: the right coronary noncoronary in two cases, and the intercoronary in one. None have truly bicuspid valves, since all three leaflet elements are present. But from the functional standpoint, these are functionally bicuspid aortic valves. The number of functional semilunar leaflets equals the number of well developed commissures.

Although no pulmonary outflow tract gradient was found at cardiac catheterization in two of these three cases of Type Ia, case 1 did have a 32 mm. gradient between the pulmonary infundibulum and the body of the right ventricle (Table I). Anatomically, this relatively small gradient appeared to be due to an unusually high and prominent moderator band.

In this regard it should be added that we doubt the existence of purely "functional" gradients in congenital heart disease which are widely believed to be produced by increased blood flow alone. Whenever we have thought that we have found a purely functional gradient, careful re-examination of the heart specimen has always revealed some anatomic basis for the gradient. These observations have led us to conclude that "functional" gradients are due to increased blood flow plus a minor anatomic abnormality, as in case 1 (Table I).

SUBCRISTAL VSD WITH AI AND PS (TYPE IB). Fig. 4 presents a fairly typical example (case 6, Table I). The VSD is subcristal but it is not purely a defect of the membranous septum as in Type Ia (Fig. 3) because the overlying subpulmonary conus displays a mild to moderate abnormality of the tetralogy type: hypoplasia, with secondary hypertrophy and focal endocardial thickening (Fig. 4,a). Conal hypoplasia results in deviation of the lower end of the conal septum (the crista supraventricularis, or parietal band) away from the superior commissure of the tricuspid valve —in an anterior, superior, and leftward direction. In view of the cristal deviation in Type Ib, the VSD is more than a membranous defect, because the conal septum is also involved.

Such deviation of the crista in Type Ib has three main consequences, all of which differ from Type Ia: (1) the VSD is larger, (2) pulmonary infundibular stenosis, with a mild to moderate gradient, is constant, and (3) the VSD is somewhat more anterior from the left ventricular aspect. In Type

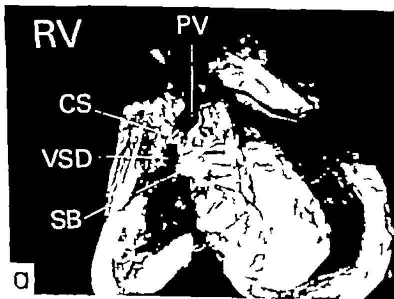


Fig. 4a. Subcristal VSD with AI and infundibular PS (Type Ib), case 6 (Table I).

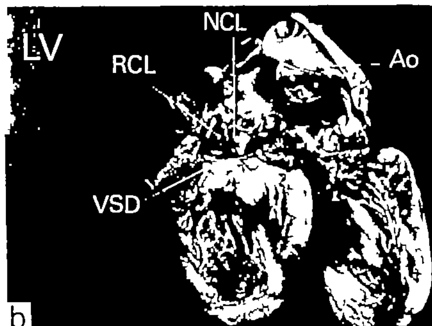


Fig. 4,b. For legend, see under Fig. 4,a.

Ia the small VSD lies with its center beneath the right coronary noncoronary commissure (Figs. 2,b and 3,c). But in Type II deviation of the crista anteriorly causes the VSD to extend more anteriorly —more beneath the right coronary leaflet than the noncoronary (Fig. 4,b).

This case is regarded as an acyanotic tetralogy of Fallot in view of the following. The cardiac anatomy definitely is of the tetralogy type (Fig. 4) including a bicuspid pulmonic valve (Table I). There was a 40 mm. gradient between the pulmonary infundibulum (40 mm. Hg) and the body of the right ventricle (80 mm. Hg). The left-to-right shunt was small (Q_p/Q_s = 2:1) with no right-to-left shunt (brachial arterial oxygen saturation 96 per cent).

In subcristal VSD with AI and PS (Type Ib) three of the four cases have underdevelopment of one aortic commissure (Table I). As in subcristal VSD with AI and without PS (Type Ia) right coronary noncoronary commissural deficiency predominates. In Fig. 4,b this commissure lies entirely below the level of the coronary ostia and some leaflet fusion is seen at this commissure, i.e., failure of leaflet separation secondary to defective commissural development. Both poorly supported aortic leaflets have prolapsed into the VSD probably largely occluding the defect during diastole. The right coronary leaflet is more prolapsed than the noncoronary apparently because the VSD lies more beneath the right coronary leaflet than beneath the noncoronary (as mentioned above concerned the effects of deviation of the crista).

A less usual example, for this series, of subcristal VSD with AI and PS (Type Ib) is presented in Fig. 5 (case 7, Table I). The subcristal VSD extends up unusually close to the pulmonary valve because of the hypoplasia of the conal septum. Also the VSD is located almost exclusively beneath the right coronary aortic leaflet reflecting the considerable anterior cristal deviation. The right coronary aortic leaflet prolapses markedly into the right ventricle, between the deviated crista above and the superior commissure of the tricuspid valve below (Fig. 5,a). Of the four cases of Type Ib (Table I) this is the only one in which the right coronary aortic leaflet herniates into the right ventricle as it always does in the Type II cases (see below). Also this is the only case of Type Ib with normal aortic commissures (Fig. 5,b). Normal aortic commissures also are characteristic in this series of Type II but not of Type I (a or b).

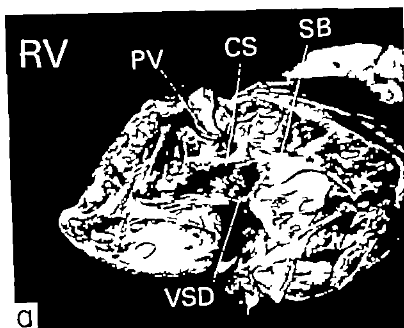


Fig. 5,a. Subcristal VSD with AI and infundibular PS (Type Ib), case 7 (Table I)

Parenthetically it should be emphasized that although this is the largest series of autopsied cases of VSD with AI yet reported by any one group, to our knowledge nonetheless the numbers within each type are exceedingly small (Table I). Hence statements of frequency which are intended to refer only to this series, should not be construed as necessarily reflecting with accuracy the condition of VSD with AI as a whole since this series is a statistically insignificant sample. In view of the frequent difficulty of ascertaining the relevant anatomic data with certainty from the literature generalizations concerning VSD with AI as a whole will be avoided.

Although the VSD in this case (Fig. 5) seems moderately large based on postmortem measurements (1.5 by 0.5 cm, Table I) its effective size must have been considerably reduced in life by herniation of the right coronary leaflet of the aortic valve. Indeed the Q_p/Q_s was only 1.4/1 with a right ventricular systolic pressure of 37 mm Hg.

SUBPULMONARY VSD WITH AI (Type II) is shown in Fig. 6 (case 9, Table I). The space above the septal band and below the pulmonary valve is wide open. Normally this space is largely filled by the conal septum, the lower rim of which usually is called the crista supraventricularis, or the parietal band. This normal situation is well seen in Type Ia (Figs. 1 to 3).

Hence, the subpulmonary VSD is a conal septal defect. This kind of VSD has been described [1-25] as anterior to the crista. However, it seems more accurate to view this as a defect *of* the crista supraventricularis—*within* it. Indeed, in the present case (Fig. 6) the aortic and pulmonic leaflets adjacent to the aorticopulmonary septum are in direct fibrous continuity because there is no interposed subpulmonary conal septal musculature to separate them.

The high subpulmonary VSD doubtless was not as large in life as it appears in Fig. 6,a because the right coronary leaflet (torn postmortem) herniates through this defect. The right ventricular systolic pressure (50 mm Hg) was not nearly systemic (150/30 mm Hg femoral artery) but the left-to-right shunt was large (Q_p/Q_s = 5.6/1). There was a 15 mm Hg gradient between the main pulmonary artery (35 mm Hg) and the body of the right ventricle (50 mm Hg) almost certainly produced by herniation of the right coronary aortic leaflet through the subpulmonary

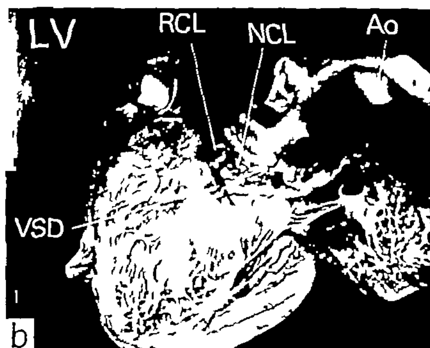


Fig. 5,b For legend see under Fig. 5,a

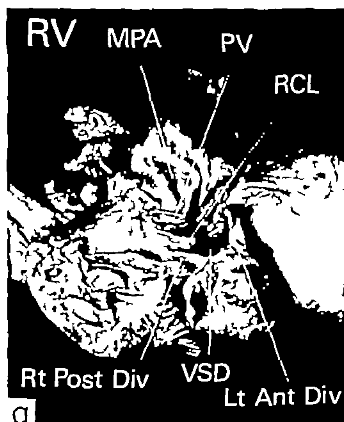


Fig. 6,a Subpulmonary VSD with AI (Type II), case 9 (Table I).

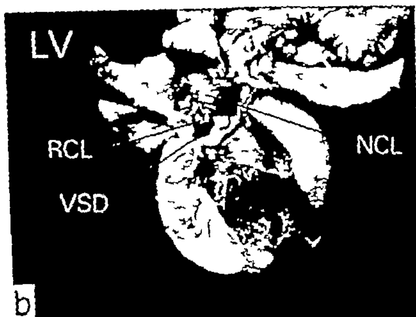


Fig. 6,b For legend see under Fig. 6,a

VSD into the right ventricular outflow tract. No other anatomic basis for this small gradient was found.

From the left ventricular aspect (Fig. 6,*b*) the VSD is seen to be entirely beneath the right coronary aortic leaflet, much *more anteriorly* than when the VSD is subcristal (Type I) (Figs. 1, 2,*c*, 3,*b*, 4,*b* and 5,*b*).

In an effort to indicate the spectrum of subpulmonary VSD with AI (Type II), another case is presented in Fig. 7 (case 11, Table I) which shows several significant differences on comparison with the previous case. The subpulmonary VSD is relatively smaller. The pulmonary outflow tract gradient was greater (50 mm. Hg). The left-to-right shunt was much less (Q_p/Q_s = 1.3:1). Indeed, the greatly ballooned and herniated right coronary aortic leaflet largely fills the VSD from the right ventricular aspect (Fig. 7,*a*) and obscures it from the left ventricular aspect (Fig. 7,*b*).

None of the four cases of subpulmonary VSD with AI (Type II) had commissural underdevelopment (Table I). Hence none had bicuspid aortic valves. All had pulmonary outflow tract gradients, subvalvular in location, and mild to moderate in degree (15 to 50 mm. Hg). These gradients all are believed to have been produced by herniation of the right coronary leaflet of the aortic valve through the subpulmonary VSD into the right ventricular outflow tract as mentioned above. None had pulmonary valvular stenosis, nor muscular subvalvular stenosis. These anatomic findings led us to accept the paradox of pulmonary infundibular stenosis produced by the right coronary leaflet of the aortic valve.

The accuracy of the foregoing interpretation is strongly corroborated by the findings of Robinson, Fell and Jacobson[4] at open heart surgery in a case of subpulmonary VSD with AI. "With release of the aortic clamp, the aneurysmally dilated right aortic cusp herniated into the right ventricle (Fig. 2) and the field was rapidly flooded by a regurgitant flow of aortic blood."

Three of the four cases of subpulmonary VSD with AI (Type II) had prolapse of the right coronary leaflet only (Table I). One showed some prolapse of the noncoronary leaflet as well, but it was much less involved than the right coronary leaflet. With subpulmonary VSD and AI, the marked predilection for prolapse of the right coronary leaflet and the massive degree of prolapse both contrast sharply



Fig. 7,a Subpulmonary VSD with AI (Type II), case 11 (Table I).



Fig. 7,b For legend see under Fig. 7,a

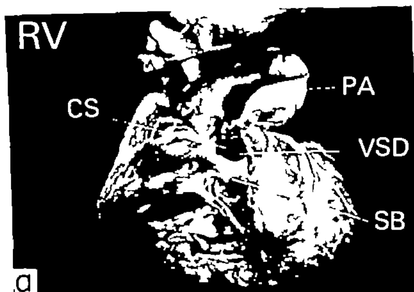


Fig. 8,a Subpulmonary VSD without AI. Age at death was three months.

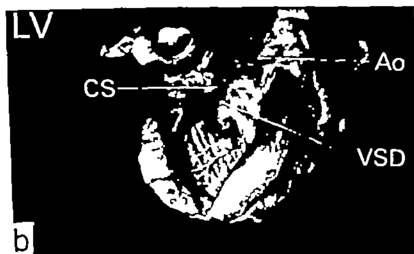


Fig. 8,b For legend see under Fig. 8,a.

with subcristal VSD and AI. In the latter both the right coronary and the noncoronary leaflets usually are involved but neither to such an extreme degree. The right coronary leaflet seldom prolapses into the right ventricle when the VSD is subcristal.

These distinctive differences between subpulmonary and subcristal VSD with AI appear to be related to the different VSD-aortic valve relations in the two types: VSD exclusively beneath the right coronary aortic leaflet with subpulmonary defects and VSD usually beneath both the right coronary and the noncoronary aortic leaflets with subcristal defects. These differing VSD-aortic leaflet relations in turn are governed by the basic differences in conal anatomy between the two types: normal or hypoplastic subpulmonary conus with subcristal defects and defective or absent subpulmonary conal septum with subpulmonary defects.

Subacute bacterial endocarditis occurred

with both types but was relatively commoner with subpulmonary VSD (2 4 cases) than with subcristal VSD (1 7)

Discussion

An important and puzzling question has long been the following Why do some patients with VSD develop AI whereas most do not?

By way of introduction to this question Nadas and associates[8] found that of 756 patients with VSD studied at this hospital between 1948 and 1962 only 34 developed AI (4 5 per cent) Since the clinical signs of AI (protodiastolic blow and wide pulse pressure) were not discovered during the first year of life in 18 carefully followed patients, they[8] concluded that AI is an acquired complication of VSD not a congenital abnormality per se Subsequently Halloran Talner and Browne[1] reported 12 patients with VSD and AI in one of whom the diastolic murmur was first heard at six months of age

The findings of the present study indicate that there are three main factors of importance concerning aortic competence all of which are related to normal aortic leaflet support (1) normal support from above (commissures) (2) normal support at the leaflet level (leaflet apposition during diastole) and (3) normal support from below (conal septum)

Although AI appears always to be acquired postnatally[8] its anatomic basis is one or more congenital malformations involving aortic leaflet support.

1 NORMAL COMMISSURES Subcristal VSD with AI (Type I) indicates the importance of normal commissural development (Table 1) In five of these seven cases the occurrence of AI appeared directly related to deficiency or absence of one commissure the exceptions being case 3 (Fig 3) and case 7 (Fig 5) which will be considered subsequently

2. LEAFLET APPOSITION Case 3 (Fig 3,c) indicates the importance of normal apposition of the closing margins of the aortic leaflets during diastole. Normally each leaflet helps to support both of its neighbors. The leaflets lean on each other as numerous pulse-duplicator studies have shown In case 3 the leaflets do not appose but this may well have resulted from absence of the intercoronary commissure as mentioned previously

3 CONAL SEPTUM The four cases with subpulmonary VSD with AI (Type II) and case 7 (Fig 5) with subcristal VSD AI and PS (Type Ib) indicate the importance of support from below by conal musculature. Herniation downward of the right coronary aortic leaflet is somewhat analogous to an indirect inguinal hernia a fibrous sausage-shaped diverticulum being protruded through a muscular defect into a region of lower pressure.

With a subpulmonary VSD the right coronary aortic leaflet is ideally aligned for herniation into the right ventricular outflow tract because the defect lies immediately beneath the entire length of this leaflet By contrast with a subcristal VSD the defect typically lies beneath approximately half of each leaflet on either side of the right coronary noncoronary commissural region This seems to explain the marked herniation of the right coronary leaflet with a subpulmonary VSD and the usually much milder herniation of this leaflet with a subcristal VSD Occasionally however marked herniation of the right coronary aortic leaflet may occur with a subcristal VSD if the crista supraventricularis is deviated sufficiently anteriorly so that the defect lies almost exclusively beneath the right coronary leaflet, as in case 7 (Fig 5) Thus, the VSD-aortic leaflet relation with subcristal VSD and PS occasionally may closely resemble that of subpulmonary VSD

Does subpulmonary VSD occur without AI? It may as Fig 8 illustrates. In this case the conal septum is not deficient immediately beneath the aortic annulus, there being a thin rim of conal musculature, 0 2 cm high supporting the aortic valve from below (Fig 8,b) The presence of some supporting conal septal musculature may perhaps explain the absence of anatomic evidence of AI However this patient died at only three months of age. Had he survived longer AI might have developed. Hence Fig 8 may well be the picture of subpulmonary VSD prior to the development of AI

Consideration of cases with a subcristal VSD and considerable hypoplasia of the conal septum as in Fig 5 side by side with cases having a subpulmonary VSD

as in Fig 8 strongly suggests that the only difference between these two types of VSD is the degree of hypoplasia of the conal septum When conal septal under development is moderately marked the anatomic result is a subcristal VSD (Fig 5) But when the conal septum is exceedingly hypoplastic the anatomic result is a subpulmonary VSD (Fig 8) Thus, the thing which makes the various types of high (subaortic) VSD look so different from the right ventricular aspect is the roof (conal musculature) The floor (ventricular septum and septal band) is a constant

Do commissural anomalies of the aortic valve occur without the development of AI They do as is indicated by the now familiar cases of bicuspid aortic valve which may have no AI and which are unusually prone to the development of calcific aortic stenosis.[13] Patients with a bicuspid aortic valve and no AI who are well until the onset of aortic stenosis, have no VSD To our knowledge all patients with a bicuspid aortic valve and a VSD develop AI sooner or later These observations suggest that Type I is not purely a commissural deficiency problem The presence of a subcristal VSD also appears to play a role in the pathogenesis of the AI in this type

It is noteworthy that in all of the recognized forms of VSD with AI the great arteries are normally related We are aware of no case of transposition of the great arteries with VSD in which AI developed In addition to the duration of postnatal life required for clinically evident AI to develop (usually more than one year) [2] there appear to be other significant factors militating against the development of AI in transposition with VSD (1) Except for cases with aortic outflow tract stenosis, aortic commissural anomalies with transposition are conspicuously rare (2) The characteristic subaortic conus of transposition supports the aortic valve from below Thus neither of the main AI predisposing factors is present in transposition with VSD

Diagnostic implications Can one diagnose the three anatomic types of VSD with AI? Although we do not have the angiocardiographic data to answer this question with certainty the anatomic findings do raise a number of points which appear very promising

(1) If aortic root injection shows AI with aneurysmal herniation of the right coronary aortic leaflet into the right ventricular outflow tract and if selective left ventricular injection reveals no crista supraventricularis, with the VSD jet extending right up to the pulmonary valve, and if a pulmonary outflow tract gradient of moderate degree or less is present—then this is subpulmonary VSD with AI (Type II Fig 1)

The problem we anticipate concerning the foregoing is that the herniated right coronary aortic leaflet might produce a filling defect resembling a crista supraventricularis following left ventriculography However this crista should appear bizarre and fluctuating with diastolic accentuation. The aortic root injection should prevent confusion by demonstrating the true nature of this crista, namely a herniated right coronary aortic leaflet.

If no left-to-right shunt is demonstrated one might be tempted to conclude that one is dealing with an unruptured sinus of Valsalva aneurysm of the right coronary sinus, and that a VSD is not present However failure to demonstrate a shunt with severe AI does not necessarily mean that no VSD is present because a defect may be plugged by prolapsed aortic leaflet tissue [11]

(2) If aortography reveals AI but without herniation of the right coronary aortic leaflet into the right ventricle, and if the VSD jet with selective left ventriculography is distinctly subcristal and not subpulmonary then this is subcristal VSD with AI (Type I Fig 1)

If the VSD is small the right ventricular pressure normal and with no pulmonary outflow tract gradient as a rule then this is subcristal VSD with AI and without infundibular PS (Type Ia Fig 1) If necessary this may be confirmed by selective right ventriculography demonstrating a normally located crista, without deviation Based upon our data the clinical and laboratory picture of Type Ia is AI with a *maladie de Roger* kind of VSD—small in size, subcristal in site

If the VSD is moderately large with mild to moderate elevation of right ventricular pressure mild to moderate pul-

monary outflow tract gradient, subcristal VSD, and mild to moderate deviation of the crista in a tetralogy of Fallot direction (anteriorly, superiorly, and to the left), then this is subcristal VSD with AI and infundibular PS (Type Ib, Fig. 1). The clinical and laboratory picture of this type is that of AI with acyanotic (atypical) tetralogy of Fallot.

Thus, with available techniques and an understanding of the anatomy, it should be possible to recognize the three types of VSD with AI.

Surgical implications. Subpulmonary VSD with AI may be successfully managed by only closing the VSD, either with an Ivalon patch, as in the case of Robinson, Fell, and Jacobson, or by direct suture as in one of our living patients not included in this study. Direct suture may provide somewhat better support to the aortic valve than patching the defect, because patching leaves the muscular margins of the VSD still widely separated. However, if the prolapsed right coronary aortic leaflet cannot readily be separated from the margins of the defect (as in the case of Robinson, Fell, and Jacobson), then patching is the only feasible course.

Since subpulmonary VSD with AI may be cured by VSD closure, this indicates that this type, in essence, is an aortic valve hernia due to defective muscular support from below, but with normal *fibrous* support from above—normal commissures. In this type, a basically normal aortic valve regurgitates because it herniates. Hence treatment of the hernia, not the valve, is indicated.

Subcristal VSD with AI, with or without PS, poses essentially the opposite surgical problem: an abnormal aortic valve (one defective commissure, usually the right coronary-noncoronary) but with little or no right ventricular herniation of the aortic valve. Consequently, in this type it is to be expected that VSD closure alone does not cure the AI. Plication of the large combined leaflet may shorten it, correcting its prolapse and permitting apposition with the other aortic leaflet of the functionally bicuspid aortic valve, thereby minimizing or abolishing the AI. If the prolapsed combined leaflet is very elongated, then plication may fail.[5] The aim of plication should be to produce apposition of the two leaflets. If significant pulmonary infundibular stenosis is present (Type Ib), it should be resected.

Our data suggest that subcristal VSD with AI may be commoner than subpulmonary VSD with AI, and the former is technically more demanding in view of the necessity of aortic valvuloplasty. As mentioned above, aortic valvuloplasty may not be successful if the prolapsed leaflet is markedly elongated, thickened, and relatively immobile. The role of aortic valve replacement by prosthesis or homograft, particularly in pediatric patients, awaits future assessment.

From the surgical standpoint, it would be only a slight over-simplification to conclude that subcristal VSD with AI (Type I) is a defective commissure problem, and that subpulmonary VSD with AI (Type II) is an aortic valve hernia. The mechanisms of AI predisposition are not entirely type specific, however. Occasionally, Type Ib (case 7, Fig. 5) may develop AI for Type II reasons (right coronary leaflet hernia). The converse, while conceivable, is not documented by available data (no case of subpulmonary VSD with AI due to a deficient commissure).

The indications for surgery are not entirely clear at present in view of current ignorance of the natural history of VSD with AI. However, available clinical and anatomic evidence *strongly suggests that* AI with VSD generally is a progressive lesion. This appears particularly probable in view of its main causes: a defective commissure or a hernia.

Consequently, we presently think that all patients with a VSD, no matter how small it is (bearing in mind Type Ia), should be followed with care in order to facilitate early diagnosis and early surgery before the aortic valve and the left ventricular myocardium have been damaged beyond recall.

In view of the differences in surgical management, preoperative diagnosis of the anatomic types of VSD with AI is of practical clinical importance.

Summary

A series of 11 postmortem cases of ventricular septal defect (VSD) with *aortic*

insufficiency (AI) was presented and an anatomic classification of VSD with AI was proposed

There are two principal anatomic types VSD beneath the crista supraventricularis (Type I) and VSD beneath the pulmonary valve (Type II)

With a subcristal VSD (Type I) there are two subtypes without pulmonary infundibular stenosis (Type Ia) and with pulmonary infundibular stenosis (Type Ib)

Subcristal VSD with AI (Type I) occurred in seven cases. In six of these the development of AI appeared basically to be related to the underdevelopment of one aortic commissure, usually the right coronary-noncoronary (4 6 cases) A functionally bicuspid aortic valve resulted in five cases. No pulmonary infundibular stenosis (Type Ia) was found in three cases, while four displayed mild to moderate pulmonary infundibular stenosis (Type Ib) The clinical and laboratory picture without pulmonary stenosis was that of AI with a maladie de Roger type of VSD while the picture with stenosis was that of AI with acyanotic (atypical) tetralogy of Fallot

Subpulmonary VSD with AI (Type II) occurred in four cases. The subpulmonary VSD is a conal septal defect the conal septal portion of the crista supraventricularis being absent or defective. All four cases had normal aortic commissures. AI resulted from herniation of the right coronary aortic leaflet through the large subpulmonary VSD into the right ventricular outflow tract resulting in a mild to moderate pulmonary outflow tract gradient in all

Subcristal VSD with AI with or without pulmonary stenosis, usually was an aortic commissural deficiency problem (in 6 7 cases) Subpulmonary VSD with AI always was a hernia of a basically normal aortic valve into the right ventricular outflow tract (in 4 4 cases)

Since the surgical management of the two principal types of VSD with AI is different, their differential diagnosis is of practical clinical importance

REFERENCES

1 Scott, R. C., McGuire J Kaplan, S Fowler N O Green, R. S Gordon, L. Z., Shabetai, R., and Davies, D. D The syndrome of ventricular septal defect with aortic insufficiency Am. J Cardiol. 2:530, 1958.

2. Denton, C., and Pappas, E. G. Ventricular septal defect and aortic insufficiency Report of three cases, Am. J Cardiol. 2:554, 1958.

3. Bialostozky D Espino Vela, J Fishleder B, de la Cruz, M. V and Soni, J Communicacion interventricular complicada con insuficiencia aortica. Estudio de nueve casos que simulaban persistencia del conducto arterial, Arch. Inst. Cardiol México 31:432 1961

4 Robinson, G Fell, S C and Jacobson, B E. Ventricular septal defect with aortic insufficiency A method of management, J Thoracic & Cardiovas Surg 43 785 1962.

5 Spencer F C Bahnson, H T and Neill, C. A. The treatment of aortic regurgitation associated with ventricular septal defect, J Thoracic & Cardiovas. Surg 43:222 1962.

6 Keck, E. W O Ongley P A Kincaid, O W and Swan, H. J C Ventricular septal defect with aortic insufficiency A clinical and hemodynamic study of 18 proved cases, Circulation 27:203 1963

7 Ellis, F H Ongley P A and Kirklin, J W Ventricular septal defect with aortic valvular incompetence. Surgical considerations, Circulation 27 789 1963

8 Nadas A S Thilenius, O G LaFarge, C. G., and Hauck, A. J Ventricular septal defect with aortic regurgitation Medical and pathologic aspects, Circulation 29:862, 1964

9 Plauth W H Braunwald, E Rockoff S. D Mason, D T and Morrow A. G Ventricular septal defect and aortic regurgitation Clinical, hemodynamic, and surgical considerations, Am J Med. 39:552 1965.

10 Halloran, K H Talner N S., and Browne, M J A study of ventricular septal defect associated with aortic insufficiency Am. Heart J 69:320 1965.

11 Van Praagh, R and Van Praagh, S. Isolated ventricular inversion. A consideration of the morphogenesis, definition, and diagnosis of nontransposed and transposed great arteries, Am J Cardiol. 17:395 1966

12. Edwards, J E. Congenital malformations. B Malformations of the ventricular septal complex, Gould, S E., editor Pathology of the heart, ed. 2, Springfield, Ill 1960, Charles C Thomas, Publisher p. 294

13 Soulié P di Matteo, J Caramanian, D Colonna, D and Andom, J La bicuspide aortique congénitale Arch mal coeur 53 1203, 1960.

14. Edwards, J E. Carey L S Neufeld, H. N and Lester R. C Congenital heart disease correlation of pathologic anatomy and angiocardiography Philadelphia and London, 1965 W B Saunders Company p. 712

15 Garamella, J J Cruz, A. B Heupel, W H. Dahl, J C Jensen, N K., and Berman, R. Ventricular septal defect with aortic insufficiency Successful surgical correction by the transaortic approach Am. J Cardiol. 5:266 1960

Experimental and clinical study on the lymph circulation

K. Seki, M.D., F.I.C.A.
Y. I m ne, M.D.
A. Shinou u, M.D.
K. Koide, M.D.
M. Uechi, M.D.
K. Mo i, M.D.
M. Nagasuka, M.D.
Y. Yoshio hi, M.D.
Tokyo, Japan

Consistent with the argument that the extravascular protein is removed from tissue chiefly via lymphatics, Hollander and associates, found the rate of disappearance of ¹³¹I albumin radioactive iodinated serum albumin (RISA) from the subcutaneous tissue was reduced in lymphedema and increased in other types of edema. Emmett and colleagues[a] also observed reduced tissue clearance rate in lymphedema. They suggest this clearance rate might be used as an index of lymphatic flow.

Threefoot and Kossover, Taldino and Hyman, and others have presented evidence for lymphaticovenous anastomoses other than thoracic duct and right lymphatic trunk–subclavian vein route. Although such alternate paths may function to transport protein from subcutaneous tissue into the vascular system, a direct passage across the wall of the blood capillaries has not yet been shown.

The factors influencing the rate of disappearance of macromolecules from tissue have been the subject of several studies. For example, Taldino and Hyman demonstrated that the rate of removal of dye labeled protein from *muscle* depended upon the rate of local tissue fluid formation and drainage via lymphatics. However, parallel information on how the state of connective tissue can modify tissue clearance rate and how injected macromolecules affect this tissue is still lacking.

The purpose of the present study is (1) to determine if extravascular protein can be removed from subcutaneous connective tissue of the leg into the nearby blood vessels, (2) to examine the changes in tissue clearance of RISA in various diseases with altered subcutaneous tissue, and (3) to examine the influence of the injected macromolecules on the tissue clearance rate.

Method and materials

Animal studies. Dogs weighing 10 to 15 kilograms were studied. Canine serum albumin labeled with ¹³¹I was obtained from Daiichi Kagaku Company, Japan. Total radioactivity and radioactivity in

From the First Department of Internal Medicine, University of Tokyo, Faculty of Medicine, Tokyo, Japan.
Received for publication June 11, 1962.

the supernatant of blood samples was measured by a scintillation counter model 100 with a 2.5 cm collimator made by the Institute of Physical and Chemical Research Japan.

EXPERIMENT 1 The hind limb of a dog with as many of the branches and collaterals of the femoral artery and vein as possible ligated was arranged for cross-circulation. ^{131}I albumin was injected subcutaneously into the distal part of the operated leg of the recipient dog (B) (Fig. 1).

EXPERIMENT 2 Except for the femoral artery and vein all the tissue of a hind limb of a dog was completely cut, with careful ligation to stop hemorrhage and escape of tissue fluid from the wound. ^{131}I albumin was injected subcutaneously into the distal part of the limb several hours after operation (Fig. 2).

Human subjects Studies were made on 12 healthy hospitalized students as controls and on 106 hospitalized patients with or without edema. These patients had heart failure (7 cases), nephritis and nephrotic syndrome (15 cases), hepatic diseases (13 cases), lymphedema (3 cases), hyperthyroidism (7 cases), myxedema (6 cases), malabsorption syndrome (2 cases), scleroderma (6 cases), paralysis agitans (7 cases), lymphosarcomatosis (6 cases), diabetes mellitus (6 cases), anemia (5 cases), leukemia (8 cases), peripheral and central paralysis (8 cases), and edema of unknown cause (7 cases).

All subjects were kept at bed rest during the several days of the experiment. ^{131}I human serum albumin, ^{131}I-human serum globulin (Daiichi-Kagaku Co.), and ^{131}I labeled polyvinylpyrrolidone (^{131}I PVP) (Raovin Abbott Co., average molecular weight 40,000) were used.

Subcutaneous injections of 3 to 4 μc of the labeled macromolecules were made in the pretibial area. Volumes of 0.03 c.c. or less were deposited with a 25 gauge needle, 3 to 4 cm. beyond the puncture site to prevent leakage of radioactive material. The scintillator was positioned with the opening of its 2.5 cm. collimator located to monitor the injection site directly. Hyaluronidase in 0.05 c.c. of saline was mixed with 0.03 c.c. of RISA containing 3 to 4 μc of radioactivity and injected into the subcutaneous tissue of a lower leg. 0.08 c.c. of RISA showing 3 to 4 μc of radioactivity was injected into the corresponding site of the contralateral leg at the same time. The clearance rate of RISA of both lower legs was compared.

The recorded radioactivity was corrected for background by subtracting the radioactivity of the corresponding part of the uninjected limb. Radioactivity in daily total urine, in samples of plasma, and in the thyroid gland were monitored. Blood was taken from the patients three

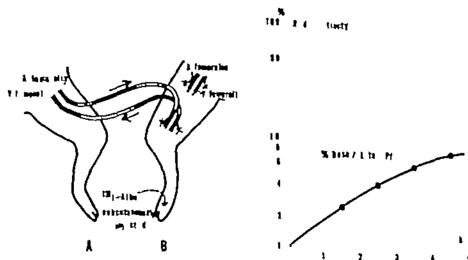


Fig. 1. Cross circulation between two dogs (A and B). Right figure shows radioactivity in plasma of dog (B).

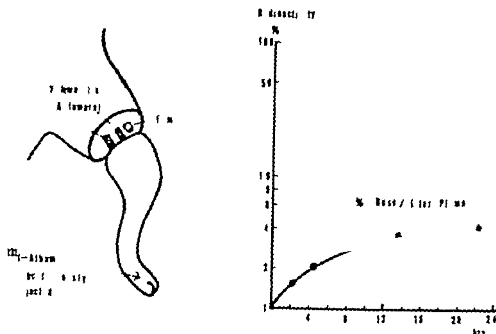


Fig. 2. Right figure shows radioactivity in plasma after subcutaneous injection of ^{131}I-albumin.

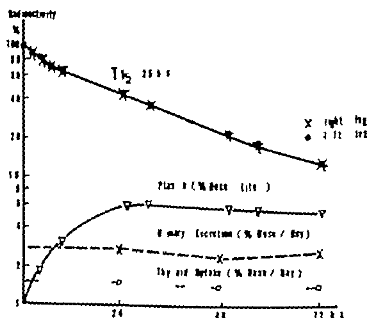


Fig. 3. A. T. ... oman 24 ... ears of age. Clearance of RISA from the subcutaneous tissue of normal right and left leg. Radioactivity in plasma, urinary excretion, and thyroid uptake.

to five times during two days and each time 25 to 30 c.c. of blood was sampled so much blood could not be so often taken from a single patient. Radioactivity in 10 c.c. of plasma was measured (it was very little) and was estimated in per cent dose per plasma liter e.g. multiplied by 100. Therefore the error might be great. This may be one of the reasons why the radioactivity in plasma of hyperthyroidism appeared accidentally almost the same as that of normals in the case of Fig. 8. The rate of clearance of ^{131}I albumin from the subcutaneous tissue of a leg was compared

Table I

N	*Subjects*	*Age*	*Sex*	*Tissue clearance (RISA) (hr)*
1	N S	21	♀	20 0
2	K T	18		33 0
3	I M	64		21 5
4	N S.	28	♀	23 0
5	T K.	40		28 5
6	O M	25		26 0
7	Y T	64	♀	30 0
8	T F	31	♀	29 5
9	Y E	40	♀	28 5
10	M E.	46	♂	22 0
11	K S.	30	♀	31 5
12	M F	36	♂	23 5
	Mean			26 4 ± 4 1

Table II

N	Subjects	Age	Sex	*Tissue clearance of RISA* At rest (hr)	Exercise (hr)
1	K Y	18		24 5	20 5
2	K H	14	♀	27 8	23 5
3	I E.	66	♂	23 0	19 5
4	T M	54	♂	23 5	20 0
5	A. S.	40	♂	28 5	23 0
6	W R.	56		28 0	25 0
7	S. M	26	♀	27 5	23 5
8	Y N	38	♂	29 5	25 0
9	T T	46	♀	23 5	19 5
10	T K.	36	♀	20 2	18 5
	Mean			25.6 ± 2.9	21.8 ± 2.3

with that of ^{131}I-globulin or ^{131}I PVP from the contralateral leg

Results

Animal experiments In Exp 1 shortly after subcutaneous injection of I albumin in the distal part of the leg of the recipient dog radioactivity could be detected in the blood of the recipient dog (B) this increased rapidly Of the radioactivity in plasma 98 to 99 per cent was trichloracetic acid precipitable. Almost no radioactivity was detected in the blood of the donor dog (A) (Fig 1)

In Exp. 2 detectable but small and slowly increasing levels of radioactivity appeared in the plasma. Almost all radioactivity was trichloracetic acid precipitable (Fig 2)

Tissue clearance of RISA in normal human beings Clearances of RISA from the subcutaneous tissue of both legs of a healthy subject gave identical curves when plotted on a semilog scale as in Fig 3 The curve fell relatively rapid during the first 6 to 8 hours, then approximated a slower exponential with an average half time ($T_{1/2}$) of 26 4 hours (range from 20 to 33 hours) Finally the curve indicated an even slower exponential fall with a T of about 12 to 13 days. In this study the $T_{1/2}$ of the second phase was used as an index of distribution of injected albumin. Thyroid radioactivity monitored externally accounted for 1 to 2 per cent of the injected dose daily excretion in urine amounted to 2 to 3 per cent of the administered radioactivity The tissue clearance of RISA was accelerated by about 18 per cent, e.g from 25 6 to 21 8 hours by 2 hours of daily exercise (walking standing etc.) Data on this point are summarized in Tables I and II

Tissue clearance of RISA in various diseases The relationship between edema and tissue clearance of RISA is shown in Fig 4 In general the clearance rate was slower than normal in lymphedema and appeared to be more rapid in most other types of edema, as reported by Hollander and associates. However in some cases with edema, the clearance rate was normal while in many cases without edema, it was rapid.

Tissue clearance of RISA in various diseases, and its change with therapy are illustrated in Figs. 5 and 6 In some cases of nephrotic syndrome and nephritis, clearance of RISA was rapid while the patient showed edema and returned towards normal when edema had disappeared. However in man cases without edema clearance was found to be rapid Similar relations were found in patients heart failure and with malabsorption syndrome.

In patients with myxedema, the clearance rate was usually normal and tended to increase when thyroxine was adminis-

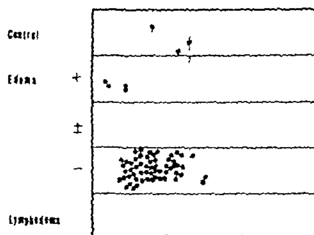


Fig. 4 Relationship between edema and tissue clearance of RISA (T)

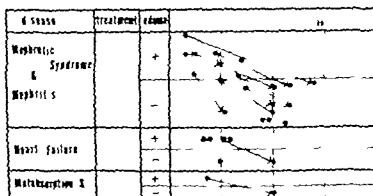


Fig. 5 Tissue clearance rate of RISA in various diseases.

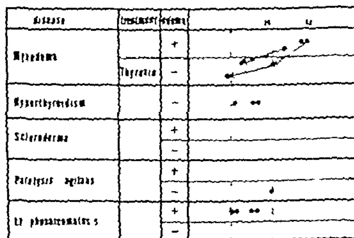


Fig. 5 Tissue clearance rate of RISA in various diseases.

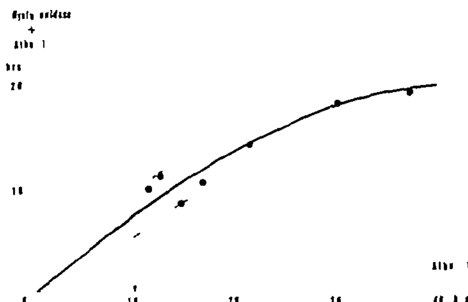


Fig. 7 Effect of hyaluronidase on the rate of clearance of RISA from the subcutaneous tissue. Each point represents measurement of T½ for albumin alone, and of T½ for albumin injected with hyaluronidase on a single patient.

tered. An injection of 0.5 c.c. of saline containing 200 Turbidity reducing unit Japan Pharmacopoeia of hyaluronidase into the subcutaneous tissue converted the nonpitting edema of myxedema into a pitting one and increased the rate of clearance of RISA from tissue (Fig. 7). In cases of myxedema with pitting edema due to coronary insufficiency clearance was rapid.

In hyperthyroidism the clearance was rapid even though uptake of ¹³¹I by the thyroid gland and urinary excretion of radioactive iodine proved to be normal during the several days following injection of RISA (Fig. 8).

In scleroderma despite hard skin and an increased amount of subcutaneous collagen fiber the clearance rate was normal when there was no edema but was rapid when there was pitting edema.

In lymphosarcomatosis, the clearance rate was usually rapid in the edematous state. The implied high lymph flow was confirmed by serial lymphangiography. In diabetes mellitus and anemia the tissue clearance rate was often rapid; in paralysis agitans, the rate was usually normal. In liver cirrhosis with ascites, the clearance rate was rapid. Of 13 cases of liver diseases, two cases with ascites and edema on the leg (liver cirrhosis and liver cancer) showed rapid tissue clearance of RISA. Of five cases of anemia, three cases (one case with edema and two cases without edema) showed rapid tissue clearance of RISA. Of six cases of diabetes mellitus, three cases showed rapid tissue clearance of RISA. Of seven cases of paralysis agitans, one case with edema showed rapid tissue clearance of RISA. Tissue clearance of RISA in peripheral and central paralysis showed no definite pattern.

The clearance of albumin from the tissues was more rapid than that of globulin. The relationship between the two in a series of subjects was almost constant (Fig. 9). The tissue clearance of PVP was *slower* than that of albumin in normal legs, but more *rapid* than the latter in edematous legs. Therefore the relationship was not linear (Fig. 10).

Comment

Although it is probably impossible to ligate all of the vascular branches and collaterals in an extremity, the results of the cross-circulation experiments in animals argue against the removal of albumin from subcutaneous tissue by *the nearby* blood vessels. Recently Threefoot and Kossover, Laldno and Hyman, and oth

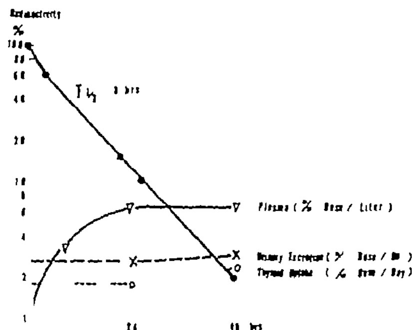


Fig. 8. K. K., man 22 years of age, had hyperthyroidism. Clearance of RISA from the subcutaneous tissue of a leg. Urinary excretion and thyroid uptake of [131]I are normal.

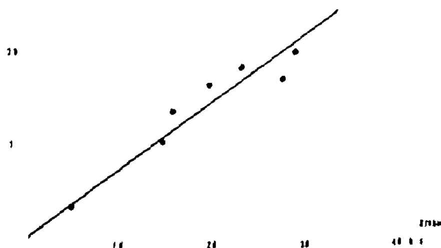


Fig. 9. Relationship between the rate of tissue clearance of [131]I-albumin and [131]I-globulin. Each point represents simultaneous measurement of albumin and globulin $T_{1/2}$ on a single patient.

ers[7,8] have presented evidence for lymphaticovenous anastomoses, which might function to convey extravascular protein through short lymph channels into the bloodstream under special conditions. But such anastomoses in subcutaneous tissue of extremities have so far been demonstrated only in two pathological cases. The results of Exp. 2 suggest that even under conditions of very high lymphatic pressure after complete lymphatic occlusion, only small amounts of albumin

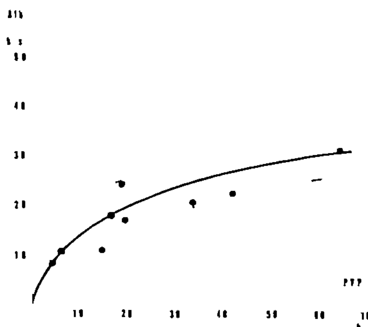


Fig. 10. Relationship between the rate of tissue clearance of ^{131}I-albumin and ^{131}I PVP. Each point represents simultaneous measurements of albumin and PVP $T_{½}$ on single patient.

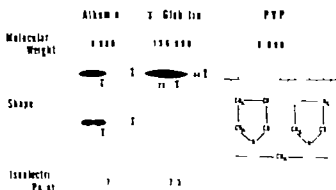


Fig. 11. Molecular weight, shape, and isoelectric point of albumin, globulin, and PVP.

find their way from subcutaneous connective tissue into the nearby blood vessels. In this experiment not only were the branches and collaterals of femoral artery and vein ligated but also all the skin, muscle, and other tissue except femoral artery and vein. The flow of tissue fluid from the wound was minimal. Jepson and co-workers detected radioactivity in plasma of a dog with lymphedema after subcutaneous injection of radioactive protein and also observed normal or increased tissue protein clearance rate and suggested that the capillary absorption is the important clearance mechanism for the protein in tissue. But in their experiments, lymphatic obstruction was incomplete. The amounts of radioiodine excreted in urine and taken up by thyroid gland were small and consistent with the metabolic breakdown of plasma protein. Thus, it appears the rate of clearance of albumin from subcutaneous tissue is an acceptable indicator of lymphatic flow under many conditions.

^{131}I albumin obtained from Abbott Com

pany or Daiichi Kagaku Company has only a small amount of inorganic ^{131}I 98 to 99 per cent of radioactive iodide of RISA is firmly combined with albumin The observation that the disappearance of radioactivity from tissue was much slower than that of inorganic ^{131}I supports the argument that the complex is stable in subcutaneous tissue

There is some possibility that the volume of injected RISA may influence the local microcirculation Warner and colleagues found that clearance of Na from muscle increased as volume was decreased from 1 to 0.01 c c Hyman and Paldino[13] found the clearance from 0.04 to 0.06 µl volumes in microcirculatory preparations was comparable to that from 0.05 c c injections in muscle In the experiments here reported there was almost no difference between the tissue clearance of 0.03 c c of RISA and that of 0.05 c.c of RISA

It is well known that lymph flow in muscle is greatly influenced by activity In our study RISA was injected into the subcutaneous tissue of the pretibial area and the subjects were all hospitalized i e kept at rest in bed Two hours of muscular activity (walking standing etc) accelerated the clearance rate by 18 per cent The daily variation in clearance rate was 5 to 10 per cent in any given subject when he was kept at bed rest throughout the experiment

As yet there is no clear explanation for the rapid phase of the clearance curve during the first 6 to 8 hours. Hollander and associates[2] suggested that it might be due to the injection of some of the RISA directly into the lymphatics or a temporary injury of the lymphatics or backflow of RISA from the opening of the injection

Although Hollander's group reported RISA clearance to be slow in lymphedema and rapid in other types of edema our experiment shows a third type of edema viz myxedema with a normal RISA clearance

In many cases of heart failure nephrotic syndrome, and malabsorption syndrome *without* edema the clearance was increased In these instances of heart diseases, venous pressure was still high and hypoproteinemia was found in nephrotic syndrome and malabsorption syndrome Since no edema accumulated in these cases, it is assumed that both tissue fluid formation and lymphatic drainage were increased

Increased tissue clearance rate in edema of lymphosarcomatous indicates that this is not lymphedema this conclusion is supported by lymphangiography Clearance of RISA was normal in scleroderma when there was no edema. This means that the proliferation of fibroblast and collagen fibers of the connective tissues does not measurably modify the rate of disappearance of such macromolecules.

Connective tissue consists of cellular elements, fibrillar elements and ground substance The last is a colloidal gel consisting of noncollagen protein acid mucopolysaccharide and carbohydrate complex. In myxedema ground substance is increased but may be restored to normal by administration of thyroxin[1] this is accompanied by the loss of several kilograms of body weight and a large diuresis. Injection of hyaluronidase converts the nonpitting edema to a pitting one. Clearance of RISA is normal in myxedema and elevated after the administration of thyroxine it is high in hyperthyroidism and is raised farther when hyaluronidase is administered These findings all suggest that the amount and the state of the ground substance play a role in keeping water in tissue and modify the disappearance of RISA. That the rapid clearance rate in hyperthyroidism is *not* due to increased metabolic breakdown of RISA is clear from the fact that thyroid uptake and urinary excretion of ^{131}I are not increased

Increased clearance of RISA in cardiac nephrotic, and other edemas may be due not only to increased passage of fluid through capillary walls, but also increased tissue permeability Rusznyák and associates[13] stated that tissue permeability was influenced by many hormones, e g cortisone desoxycorticosterone acetate (DOCA) estrogen progesterone and by many metabolic inhibitors. But the results were obtained mainly by observing diffusion rate of intradermally injected dye and therefore were not quantitative Takeda[15] observed that in a normal dog thyroxine increased tissue clearance rate of RISA while growth hormone and cortisone de

creased it Langgard showed that the tissue clearance of RISA was slightly decreased in three cases of myxedema.

The relationship between the tissue clearance of albumin and globulin may be partially due to molecular weight. The relationship between the clearance rate of PVP and albumin can be explained if it is assumed that movement of colloids depends upon molecular weight in edematous tissue, but the shape of the molecule plays some role in normal tissue. Albumin also because of its negative charge, may pass through the similarly charged mucopolysaccharide of connective tissue more readily than globulin (Fig 11)

Summary

1 Molecular weight shape and electric charge may each play some role in determining the rate of disappearance of macromolecules from subcutaneous connective tissue.

2 The state of the connective tissue especially the volume and state of its ground substance may modify the rate of disappearance of macromolecules from the tissue.

3 There are at least three types of edema tissue clearance of albumin was slow in lymphedema normal in myxedema and accelerated in other types of edema. The clearance rate was usually normal in scleroderma and rapid in hyperthyroidism and in edema of lymphosarcomatosis

4 The rate of clearance of albumin from subcutaneous tissue can be used as an indicator of lymphatic flow under usual conditions.

REFERENCES

1 Drinker C. K. Extravascular protein and the lymphatic system Ann. New York Acad. Sc. 16:807 1946
2. Hollander W Reilly P and Burrough B. A. Lymphatic flow human subjects as indicated by the disappearance of ^{131}I-labeled albumin from the subcutaneous tissue, J Clin. Invest. 40:222, 1961
3. Emmett, A. J J Barron, J N and Veal, N The use of ^{131}I-albumin tissue clearance measurements and other physiological tests for the clinical assessment of patients with lymphedema, Brit. J Plast Surg 20(1):1 1967
4 Threefoot, S. A., and Kossover M F Lymphaticovenous communications in man, Arch I t. Med. 117:213 1966
5. Paldino, R. L., and Hyman, C Relationship between lymphatic and blood flow in various structures in abdominal cavity Proc. Soc. Exper Biol & Med 117:904, 1964
6 Paldino R L and Hyman, C. Removal of small and large molecules from microinjection sites in rat skeletal muscle, Am J Physiol. 210:576, 1966.
7 Jacobson, S. and Feldman, A. Estimation of lymph flow extremities, Arch Surg 82:97 1961
8 Pressman, J J Simon, M B Hand, K., and Miller J Passage of fluids, cells, and bacteria via direct communication between lymph nodes and veins, Surg Gynec & Obst. 115:207 1962.
9 Koehler P R., and Schaffer B Peripheral lymphaticovenous anastomoses. Report of two cases, Circulation 35:401 1967
10 Jepson R P Simeone, F A and Dobyns, B M Removal from skin of plasma protein labeled with radioactiv iodine, Am. J Physiol. 175:443 1953.
11 Warner C F Dobson, E L. Pace, N Johnston M E nd Finney C R. Studies of human peripheral blood flow effect of injection volume on the intramuscular radiosodium clearance rate Circulation Res. 10:89 1962.
12. Hyman, C., nd Paldino, R. L. Local temperature regulation of microtissue clearance from rat skeletal muscle Circulation Res. 10:89 1962.
13 Rusznyak, I Foldi, M and Szabo, G Lymphatics and lymph circulation, Oxford, 1960, Pergamon Press, Ltd.
14 Asboe-Hansen G. Endocrine control of connective tissue, Mills, L. C and Moyer J H editors. Inflammation and disease of connective tissue, Philadelphia and London, 1961 W B. Saunders Company p. 38.
15. Takeda, Y Hormonal effects on lymphatic transport of i terstitial albumin in the dog, Am J Physiol. 206 1021 1964
16. Langgard, H The subcutaneous absorption of albumin i edematous st tes, Act med scandinav 173:645 1963.

Influence of bradykinin on isolated canine venous strips

V. P. DePasquale, M.D.
G. E. Burch, M.D.
New Orleans, La.

The nonapeptide bradykinin has been shown to be a powerful dilator of arteriolar smooth muscle.[1-3] Thus, the intravenous administration of bradykinin is associated with a decrease in total peripheral resistance and systemic arterial blood pressure.[-4] The influence of bradykinin on venous smooth muscle is less well known. Mason and Melmon have reported that bradykinin administration in man results in a transient increase followed by a decrease in venous tone. The initial increase in venous tone was considered to be secondary to the decrease in systemic arterial pressure, whereas the increase in tone was considered to be due to the direct effect of bradykinin on venous smooth muscle. Guth and associates, on the other hand, considered bradykinin to produce constriction of the veins in the rabbit ear. Because bradykinin is formed endogenously in man and may play an important role in autoregulation, we considered it of interest to study the action of this polypeptide on isolated, metabolically supported canine venous strips.

Material and methods

Canine venous strips about 1.0 cm. in length were mounted in a 40 ml. muscle chamber in a water bath maintained at 37° C. One end of the venous strip was fixed to the bottom of the muscle chamber by means of a fine platinum wire. The other end of the strip was attached by means of a platinum hook and monofilament to a Grass Model FT 0.03C force displacement transducer. The muscle chamber was filled with Krebs solution with the following millimolar concentrations: NaCl, 118.9; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 14.9; dextrose, 5.6; $CaCl_2$, 2.5; and sucrose, 49.9. The Krebs solution was aerated with a mixture of 95 per cent O_2 and 5 per cent CO_2. The venous strips were equilibrated under a tension of about 200 mg. for about 30 minutes before bradykinin was injected into the muscle chamber. The solution in the muscle chamber was changed according to the washout technic described by Furchgott.[8]

Femoral and mesenteric venous strips were removed from dogs lightly anesthetized with urethan. The veins were studied within one hour after removal from the animals.

The experiments were performed in the following manner. After allowing at least 30 minutes for the tension in the venous segment to become stable, 5 µg (0.125 µg per milliliter) of bradykinin was introduced into the muscle chamber. In some experiments, after the response to bradykinin developed, the water bath was

From the Department of Medicine of the Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, La.
Supported by grants from the United States Public Health Service, Russell A. [illegible] Fund for Research in Heart Disease, and the Rudolph Matas Fund for the Kate Prewitt Hess Laboratory.
Received for publication April 1, 1967.

flushed and Dibenamine or Nethalide (2 isopropylamino-1-[2 naphthyl] ethanol hydrochloride) was introduced into the muscle chamber. Following pretreatment with Dibenamine or Nethalide bradykinin was added to the muscle chamber without flushing.

A total of 15 femoral and seven mesenteric venous strips were studied. Seven of the strips (four femoral and three mesenteric) were studied after pretreatment with Dibenamine and five strips (three femoral and two mesenteric) were studied after pretreatment with Nethalide.

Results

Following the injection of bradykinin into the muscle chamber there was an increase in tension in 17 of the 22 venous strips studied (Fig. 1). In three mesenteric and two femoral venous strips, tension did not change. The tension developed by the venous strips, varied from 18 to 350 mg. (average 108 mg.). There was no significant difference in the magnitude of developed tension between mesenteric and femoral venous strips. After reaching a peak in 10 to 30 seconds, the tension began to decrease gradually, usually returning to initial levels within 5 minutes.

Pretreatment of the venous strips with Dibenamine or Nethalide did not inhibit the response to bradykinin (Fig. 2). However, after two or three responses, and occasionally after only a single contraction, the reactivity of the venous strips rapidly diminished. Increasing the concentration of bradykinin or allowing as long as two hours for recovery did not increase the sensitivity of the venous strips once tachyphylaxis had developed.

Discussion

In man bradykinin is released enzymatically from the α-2 globulin. It has been shown that bradykinin is responsible for functional hyperemia in the sweat glands and salivary glands. There is also evidence

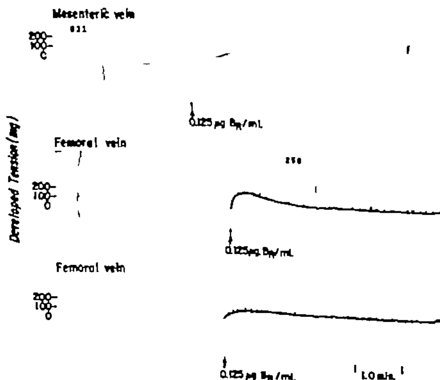


Fig. 1. Venoconstrictor effect of bradykinin (0.125 µg per milliliter) on canine mesenteric and femoral venous strips.

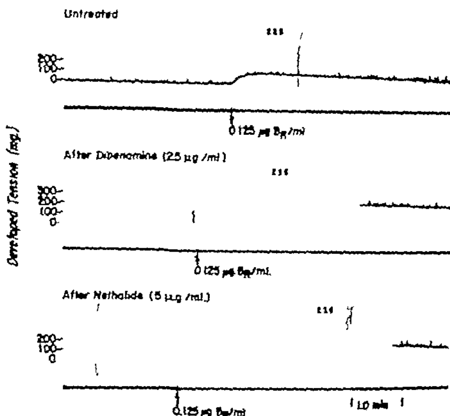


Fig. 2. Venoconstrictor effect of bradykinin (0.125 μg per milliliter) before and after α- and β-adrenergic blockade with Dibenamine and Nethalide respectively.

that bradykinin may be responsible for reactive hyperemia and it has been suggested that this polypeptide may play an important role in autoregulation of blood flow. Although it is well established that bradykinin produces relaxation of arteriolar smooth muscle (resistance vessels), the effect of bradykinin on the capacitance vessels is uncertain. The present experiments indicate that, at least in isolated venous segments, bradykinin produces an increase in tone which is not inhibited by α- or β-adrenergic receptor blockade.

The situation is more complicated in man. The intravenous infusion of bradykinin is associated with a decrease in peripheral vascular resistance and arterial blood pressure and an increase in cardiac output.[4] The decrease in arterial blood pressure is associated with a decrease in baroreceptor activity which is in turn associated with constriction of the peripheral venous bed.[11] The reflex venoconstriction results in an augmentation of systemic venous return and an increase in cardiac output. Certainly, if bradykinin dilated the capacitance vessels as well as the resistance vessels, cardiac output and arterial blood pressure would decline, probably to dangerously low levels. However, in all experiments thus far reported, infusion of bradykinin was associated with an increase in cardiac output. The present experiments suggest that in addition to reflex baroreceptor constriction of the peripheral venous bed an augmentation of cardiac output may be due to the direct venoconstrictive effect of bradykinin on the veins.

Although bradykinin produces dilatation of arteriolar smooth muscle, it does constrict intestinal smooth muscle.[3] Furthermore, from our studies on the digital circulation, we concluded that bradykinin constricted the arteriovenous anastomoses.[11] Thus, the action of bradykinin on smooth muscle varies depending upon the type

of smooth muscle. The ability of bradykinin to selectively constrict or relax vascular smooth muscle makes it an ideal agent for local vascular regulation.

Summary

The action of the nonapeptide bradykinin was studied on isolated canine venous strips. Bradykinin was found to produce an increase in tension in femoral and mesenteric venous strips which was not inhibited by α- or β-adrenergic receptor blockade. Thus while bradykinin relaxes arteriolar smooth muscle *it apparently constricts* venous smooth muscle. The ability of bradykinin to selectively relax resistance vessels while constricting capacitance vessels would make it an ideal regulator of local blood flow.

REFERENCES

1. Rocha e Silva, M., Beraldo, W. T., and Rosenfeld, G.: Bradykinin, hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin, Am. J. Physiol. 156:261, 1949.
2. Lewis, G. P.: Active polypeptides derived from plasma proteins, Physiol. Rev. 40:647, 1960.
3. Fox, R. H., Goldsmith, R., Kidd, D. J., and Lewis, G. P.: Bradykinin as a vasodilator in man, J. Physiol. 157:589, 1961.
4. Paldino, R. L., Hyman, C., and Lenthall, J.: Bradykinin-induced increase in total and effective blood flow in skeletal muscle, Circulation Res. 11:847, 1962.
5. de Freitas, F. M., Faraco, E. Z., and de Azevedo, D. F.: General circulatory alterations induced by intravenous infusion of synthetic bradykinin in man, Circulation 29:66, 1964.
6. Kontos, H. A., Magee, J. R., Shapiro, W., and Patterson, J. L.: General and regional circulatory effects of synthetic bradykinin in man, Circulation Res. 14:351, 1964.
7. Mason, D. R., and Melmon, K. L.: Effects of bradykinin on forearm venous tone and vascular resistance in man, Circulation Res. 17:106, 1965.
8. Guth, P. S., Cano, G., and Jaramillo, J.: The effect of bradykinin on vascular smooth muscle, Ann. New York Acad. Sc. 104:69, 1963.
9. Furchgott, R. F.: Spiral-cut strip of rabbit aorta for in vitro studies of responses of arterial smooth muscle, Methods M. Res. 8:177, 1960.
10. Hilton, S. M., and Lewis, G. P.: Mechanism of the functional hyperemia in the submandibular salivary gland, J. Physiol. 129:253, 1955.
11. Braunwald, E., Ross, J., Kahler, R. L., Gaffney, T. E., Goldblatt, A., and Mason, D. R.: Reflex control of the systemic venous bed, Circulation Res. 12:539, 1963.
12. Burch, G. E., and DePasquale, N. P.: Bradykinin, digital blood flow, and the arteriovenous anastomoses, Circulation Res. 10:105, 1962.

Comparison of norepinephrine and isoproterenol in experimental coronary shock

Observations on the effects of dextran infusion

Richard F. Feuron, M.D.
New Haven, Conn.

The therapy of shock following myocardial infarction (coronary shock) has involved an attempt to increase the blood pressure with drugs which constrict the arterioles through α adrenergic receptor stimulation. There is evidence, however, that drugs with only α adrenergic activity, such as methoxamine (Vasoxyl), may depress the cardiac output despite an increase in the blood pressure, whereas drugs with both α-adrenergic (vasoconstrictive) and β-adrenergic (inotropic) activity, such as norepinephrine (Levophed) and metaraminol (Aramine), may increase both the blood pressure and the cardiac output, at least temporarily. Although these latter two drugs do not uniformly increase the cardiac output in coronary shock, they are the most commonly used vasopressors in the treatment of this condition today. Whether their use has reduced the mortality rate of patients in coronary shock from 80 to 60 per cent, as initially claimed,[4] or not, as more recently claimed, is debatable. It is clear, however, that the continued high mortality rate associated with this syndrome demands further therapeutic attempts. In view of the fact that the syndrome of shock following myocardial infarction is better correlated with depression of cardiac output and contractility than depression of the systemic vascular resistance,[7,7,11] it has seemed appropriate to evaluate the hemodynamic and metabolic responses of dogs in coronary shock to drugs which act primarily to increase cardiac output by increasing myocardial contractility.

In the present study, we have compared the efficacy of isoproterenol (Isuprel), a pure β-adrenergic stimulating agent, with that of norepinephrine in the treatment of experimental coronary shock induced by microsphere embolization of the coronary arteries. We have also made observations on the effects of blood volume expansion with dextran in this situation.

Methods

Adult mongrel dogs weighing 11 to 20 Kg. were anesthetized with intravenous diallylbarbituric acid with urethane (Dial with urethane), 0.6 ml. per kilogram of body weight, and anticoagulated with intravenous heparin, 3.5 mg. per kilogram. Under fluoroscopic guidance, catheters were placed in the coronary sinus by way of the right jugular vein, in the right atrium, and inferior vena cava by way of the femoral veins, and in the descending aorta from the femoral artery. A bipolar electrode catheter was placed in the superior vena cava by way of the left jugular vein for cardiac pacing in dogs developing

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.
This work was done during tenure of a fellowship (HE 1 873-01) of the National Heart Institute, and was supported by grants from the Connecticut Heart Association and the United States Public Health Service (HE 1 HE-09560).
Received for publication July 17, 1967.

atrioventricular block or sinoatrial arrest. The aortic catheter contained a thermistor probe in order to record thermal dilution curves following injection of room temperature saline into the inferior vena cava, for calculation of cardiac output (CO).[12,13] Previous work from both this laboratory[12,13] and elsewhere[1] has demonstrated the reproducibility of the thermal dilution method and its comparability to the dye dilution technique. Statham strain gauges were connected to the appropriate catheters to measure aortic pressure (AP) and right atrial pressure (RAP). left ventricular systolic (LVS) and end-diastolic pressure (LVEDP) were measured through a metal cannula introduced into the left ventricle (see below). All gauges were placed at that height above the table estimated in each dog to represent the level of the right atrium. Limb lead electrodes were placed for electrocardiography. Recordings were made by an Electronics for Medicine recorder. Stroke work was calculated from values of stroke volume and left ventricular systolic and end-diastolic pressures. The maximal rate of rise of left ventricular pressure (LV dp/dt) was derived from the left ventricular pressure curve by a special differentiating amplifier (Electronics for Medicine). At appropriate times of stable blood pressure and cardiac output, blood samples were obtained from the coronary sinus and aortic catheters for subsequent determination of lactate (L) and pyruvate (P) content[14] and immediate measurement of oxygen saturation, pH, and hemoglobin concentration.

Cyclic positive pressure breathing of compressed air through a cuffed endotracheal tube at pressures which did not significantly affect the aortic pressure or cardiac output was used when necessary to keep arterial pH near 7.4 and oxygen saturation above 90 per cent. In nearly one half of the animals studied, oxygen consumption was continuously monitored with an open-circuit oxygen analyzer* appropriately attached either to the endotracheal tube or to the expiratory tube of the positive pressure breathing apparatus.

A double lumen, balloon tipped, metal cannula was introduced through the right common carotid artery into the left ventricle for measurement of LVS, LVEDP, and LV dp/dt. Propranolol (Inderal)* 0.125 mg. per kilogram was given intravenously followed by a constant infusion of 1.9 μg per kilogram per minute. It has been demonstrated that propranolol significantly diminishes the high incidence of early ventricular fibrillation that attends experimental coronary occlusion by microembolization. A low dose of the drug was used to minimize and shorten the duration of its depressant effects on ventricular contractility (see below). After 15 minutes of propranolol administration, baseline measurements of CO, AP, LVS, and LVEDP, RAP, and LV dp/dt were recorded and blood samples were obtained for the biochemical analyses noted above. After the metal cannula had been withdrawn to the aorta (determined by pressure change), the coronary arteries were embolized as previously described.[1] Briefly, saline was introduced through the outer lumen of the cannula to distend the balloon sufficiently to occlude the ascending aorta. Microspheres of divinylbenzene 150 to 300 micra in diameter, suspended in 15 per cent gum acacia, were then injected through the distal inner lumen. Balloon distention was maintained for 10 seconds following microsphere injection, then released. Repeated embolization was performed until the development of shock, which, for the purpose of these experiments, was defined as a 50 per cent or greater reduction in that cardiac output and stroke volume which had been measured immediately before initiation of embolization and a reduction in mean aortic pressure to 80 mm. Hg or below, both persisting for 15 minutes. As soon as it appeared that this degree of hemodynamic depression had been induced, propranolol infusion was discontinued. After shock had persisted for 15 minutes, as noted by measurement of CO and AP every 5 minutes, blood samples were obtained from the aorta and coronary sinus for determination of lactate, pyruvate, hemoglobin, pH, and oxygen saturation. The dogs were then randomly assigned to one of three groups: (1) Group A, control

*Oxford Instruments, Oxford, Mass.

*Courtesy of Dr. Alex Sahagian-Edwards, Ayerst Laboratories.

receiving no medication except lidocaine (Xylocaine) 1 to 2 mg per minute as necessary to suppress ventricular extra systoles and a constant infusion of saline at 35 c c per hour (2) Group B norepinephrine treated receiving 7 to 30 μg per minute of norepinephrine as needed to maintain the mean AP at approximately 110 to 120 mm Hg and lidocaine as described (3) Group C isoproterenol treated receiving isoproterenol 7 to 30 μg per minute in an attempt to return the cardiac output toward normal and lidocaine as described The isoproterenol infusion rate was carefully adjusted and readjusted to avoid inducing frequent ventricular extrasystoles (greater than 5 per minute) or a heart rate greater than 150 per minute

The animals in each group were observed for periods up to 4 hours. During the final hour of observation of most of the dogs in Groups B and C the mode of therapy was switched from norepinephrine to isoproterenol or vice versa and the hemodynamic and biochemical parameters mentioned were again measured

The effects of blood volume expansion with intravenous dextran in 50 c c aliquots on CO LVEDP and RAP were assessed in several dogs during isoproterenol therapy and in several dogs 2½ to 3 hours after the induction of shock when isoproterenol and norepinephrine therapy had been discontinued

To estimate the degree of β-adrenergic blockade present as a result of propranolol at the time that sympathomimetic therapy for coronary shock was begun in the shocked dogs two additional nonembolized dogs were given 0 125 mg per kilogram of propranolol followed by a 30 minute infusion of 1 9 μg per kilogram per minute in one and of 3 8 μg per kilogram per minute in the other Fifteen minutes after discontinuance of the infusion isoproterenol 0 04 to 0 11 μg per kilogram per minute was begun The responses of the SV LVS and LVEDP LV dp/dt and heart rate to each drug were noted

In two dogs one of which had not received propranolol or coronary embolization and the other of which had undergone coronary embolization 2 hours previously such that SV was reduced by 21 per cent and LVEDP equalled 30 mm Hg SV heart rate, LV dp/dt LVS and LVEDP were measured every 10 minutes for 90 minutes. Lidocaine was infused at 2 0 mg per minute between 30 and 60 minutes of this period of observation

At the conclusion of each experiment each dog was killed the chest opened and after noting the location of the catheters the heart was removed Any evidence of mediastinal hemorrhage or aortic valve damage secondary to the experimental procedure eliminated the dog from the study

Results

A total of 44 dogs underwent coronary embolization as described without complicating hemorrhage or aortic valvular damage Of these 23 developed persistent shock and were randomly assigned to the three groups mentioned 14 died before the 15 minute period of persistent shock had elapsed and 7 had less severe hemodynamic depression

Shock dogs A total of 23 dogs developed shock as defined lasting 15 minutes without rapid deterioration during that time. The average dose of microspheres in each dog was 11 6 mg per kilogram In other studies utilizing similar spheres, this dose has been noted to result in an eventual mortality rate of 100 per cent [17] The average per cent depression of both the cardiac output and stroke volume due to coronary embolization in the dogs was 65 per cent ranging from 51 to 88 per cent The average mean aortic pressure at this time was 65 mm Hg ranging from 40 to 80 mm. Hg The average systemic vascular resistance increased from 64 units before embolization to 91 units with shock The average systemic excess lactate 15 minutes after development of shock was 1.58 mmole per liter ranging from 0 32 to 3 96 mM per liter The average percentages of myocardial extraction of lactate, pyruvate and oxygen following 15 minutes of shock were 3 2 and 77 per cent respectively ranging from −15 to +24 per cent for lactate −32 to +28 per cent for pyruvate and 69 to greater than 90 per cent for oxygen

*Per cent of myocardial extraction, lactate (L)

$$L = \frac{\text{arterial concentration, L} - \text{coronary sinus concentration, L}}{\text{arterial concentration, L}}$$

Table I. Cardiac output in shocked dogs*

No.	Spheres (mg)	Base	Shock	Hr of therapy ½	1	1½	2	2½	3	3½	4
Norepinephrine Rx											
B1	6.7	3.73	0.79	1.06	1.04	1.04	1.12	1.16	1.04	0.75	Death
B2	10.0	1.49	0.28	0.48	0.50	0.70	0.65	0.65	0.86	0.88§	1.50‡
B3	16.7	2.30	0.47	0.52	0.61	0.55	0.56	0.50	0.60	1.40‡	1.70*§
B4	6.7	3.00	1.00	1.29	0.74	0.97	1.31	1.00	1.46‡	3.22‡	
B5	16.7	2.60	1.11	0.73	0.71	0.82	0.75	1.00‖	2.54‡	2.79*	1.04§
B6	10.0	2.39	1.16	1.13	1.27	0.81	V.F.				
B7	10.0	3.66	1.63	1.53	2.00	2.38	1.14	1.24	Pulmonary edema		
Mean†	11.0	60	0.92	0.96	1.1	1.04	0.92	0.91	0.83		
±S.D.	4.2	0.66	0.45	0.40	0.79	0.57	0.30	0.10	0.42		
Isoproterenol Rx											
C1	10.0	1.44	0.59	0.93	1.33	1.31	1.28	1.90§	2.10	Death	
C2	6.7	2.66	0.62	1.80	1.70	1.74	1.90	2.37	Death		
C3	10.0	2.55	0.73	2.06	2.60	3.00	2.96	3.36	3.13	Death	
C4	18.4	2.96	1.09	1.59	1.50	1.20	1.43	V.F.	Off lidocaine		
C5	13.3	2.94	0.83	1.86	1.70	Death					
C6	3.3	2.44	1.00	36	2.76	2.85	2.87	1.08‡	0.96	1.00§	
C7	17.0	3.14	1.03	1.25	1.70	2.24	2.97	3.34	3.68	1.02‡	1.23
C8	13.0	2.97	0.40	2.08	2.77	3.34	4.45§	V.F.			
Mean†	14.0	2.61	0.78	1.70	2.01	24	2.34	2.79	93		
±S.D.	5.6	0.55	0.35	0.46	0.60	0.85	1.10	0.80	0.90		

*Liter per minute; each value represents the average of at least two determinations.
†Mean cardiac output levels do not include values when a sympathomimetic Rx has been changed or discontinued.
‡Following change of Rx to norepinephrine or isoproterenol.
§Following lidocaine infusion.
‖Following discontinuance of Rx.

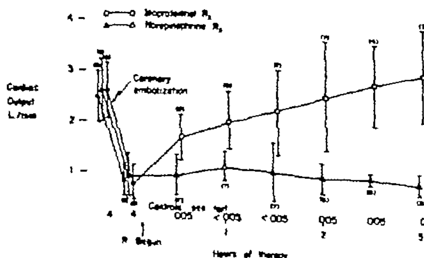


Fig. 1. Mean values of cardiac output ±1 S.D. in each group of dogs at rest, following coronary embolization and in response to isoproterenol or norepinephrine. At each half hour the cardiac output is significantly greater in isoproterenol treated dogs than in norepinephrine treated dogs. Numbers in parentheses refer to number of dogs.

Isoproterenol R_x
Norepinephrine R_x
Coronary embolization
Stroke volume ml/beat
Controls see text
p > 25 > 25 < 01 < 005 < 01 < 005 < 005 < 005
R_x Beg n
1 2 3
Hours of therapy

Fig 2 Mean lues of strok olume ± 1 S D each group of dogs t rest followi g coronary embolization, nd in response to isoproterenol or norepinephrine. At each half hour the strok volume is significa tly greater in isoproterenol treated dogs tha in norepinephrine treated dogs. Numbers i parentheses refer to number of dogs

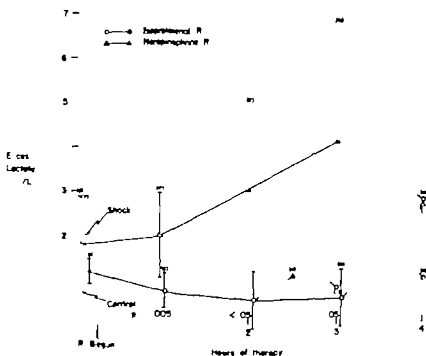


Fig 3 Mean alues of ystemic excess lactat ± 1 S D i ach group of dogs 15 minutes after coronary embolization had produced shock nd t hourly i terv ls i response t isoproterenol or norepinephrine At each hour the systemic excess lact t is significantly less i isoproterenol treated dogs tha in norepinephrine treated dogs Change of therapy in five dogs (broken lines) result in reversal of ystemic excess lact t levels in each.

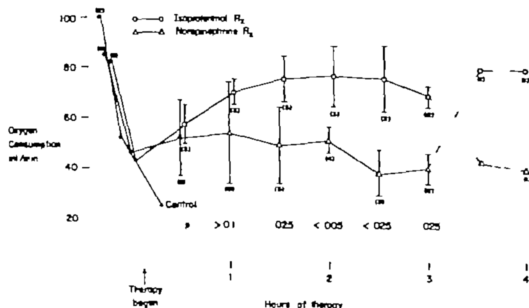


Fig. 4. Mean values of total body oxygen consumption ± 1 S.D. in each group of dogs at rest, following coronary embolization, and in response to isoproterenol or norepinephrine. At each half hour after the first hour of therapy the oxygen consumption is significantly greater in isoproterenol treated dogs than in norepinephrine treated dogs. Change of therapy in two dogs (broken lines) results in reversal of oxygen consumption values in each.

The 23 dogs were randomly assigned to serve as controls—8 dogs, to receive norepinephrine therapy—7 dogs or to receive isoproterenol therapy—8 dogs as outlined. There were no significant differences among the three groups in either the per cent of change or the absolute levels of cardiac output, stroke volume, blood pressure, systemic vascular resistance, oxygen consumption, or systemic excess lactate (Table I, Figs. 1 to 4).

Control Group A. Of the eight control dogs, six died during the subsequent 30 minutes of observation, two with ventricular fibrillation despite the use of lidocaine and four with progressive hypotension and eventual electrical standstill unresponsive to endocardial pacing. One of the latter four received isoproterenol for 5 minutes with a doubling of the cardiac output and blood pressure. When the drug was discontinued, there was progressive hypotension and standstill. Of the other two dogs in the control group, one showed a further drop in cardiac output and died with ventricular fibrillation despite lidocaine administration at 36 minutes of observation; the other was observed for 3 hours with only lidocaine therapy as needed to suppress ventricular irritability. In this latter dog, severely reduced cardiac output and stroke volume persisted during this time with a further increase in excess lactate. At 3 hours, therapy with intravenous dextran and then isoproterenol reversed these parameters toward normal.

Norepinephrine Group B. Seven dogs received a constant infusion of norepinephrine sufficient to keep the mean aortic blood pressure near 110 to 120 mm. Hg. Further elevation of this pressure to 130 mm. Hg or lowering to 100 mm. Hg by appropriate adjustments of the infusion rate was not found to consistently affect the cardiac output or stroke volume. All dogs survived at least 1½ hours. The average dose of norepinephrine was 1 μg per kilogram per minute, ranging from 0.5 to 2.0 μg per kilogram per minute, with the higher amounts often being necessary to maintain the blood pressure later in the period of observation. One dog (Table I, No. B6) died at 1½ hours with ventricular fibrillation despite the concomitant use of lidocaine. A second dog (Table I, No. B7) died in pulmonary edema with bloody tracheal froth at 2½ hours. In the other five dogs, norepinephrine was discontinued

at 2½ to 3 hours at which time isoproterenol and dextran were given to four of these (Nos. B2 to 5) and in the fifth (No. B1) discontinuance of levophed led to death.

Although the desired blood pressure response to norepinephrine was attained and no dogs died during the first 1½ hours, the cardiac output and stroke volume in the group as a whole did not significantly increase during the period of observation (Table I, Figs. 1 and 2). The average systemic vascular resistance increased from 93 to 150 units with institution of norepinephrine. The mean systemic excess lactate showed a progressive rise (Fig. 3). The oxygen consumption was followed in five dogs and the mean value for the group showed an initial increase from 53 to 60 per cent of the baseline level with initiation of norepinephrine and a subsequent gradual decline during continued norepinephrine therapy (Fig. 4).

After 2½ to 3 hours of norepinephrine infusion isoproterenol was administered to four dogs. In each instance where measured cardiac output was more than doubled (four dogs, Table I), the systemic excess lactate was significantly reduced (three dogs, Fig. 3), and the oxygen consumption was significantly increased (one dog, Fig. 4).

Isoproterenol Group C. Eight dogs received isoproterenol in an attempt to return the depressed cardiac output toward normal without inducing ventricular irritability or sinus tachycardia greater than 150 per minute. The average dose of isoproterenol used was approximately 1 μg per kilogram per minute, ranging from 0.5 to 2.0 μg per kilogram per minute. Two dogs (Table I, Nos. C4 and C8) died of ventricular fibrillation during isoproterenol infusion, both after 2 hours of therapy. In one of these lidocaine was inadvertently discontinued 3 minutes before the arrhythmia, and in the other excessive amounts of isoproterenol were being given such that the cardiac output had been increased tenfold and the stroke volume ninefold to levels 45 to 50 per cent greater than the pre-embolization values. Four other dogs died promptly with progressive hypotension when isoproterenol was discontinued after 1, 2½, 3, and 3½ hours of treatment, indicating the need for the drug in this group at each hour of therapy. All dogs responded to isoproterenol with a significant and sustained increase in cardiac output and stroke volume (Figs. 1 and 2). The mean systemic excess lactate for the group progressively declined (Fig. 3); oxygen consumption progressively rose in the three dogs in which it was measured (Fig. 4). The average mean aortic blood pressure increased from 64 to 100 mm. Hg with institution of isoproterenol therapy despite a coincident drop in average systemic vascular resistance from 88 to 64 units. The cardiac output and stroke volume of the isoproterenol treated dogs at each ½ hour of therapy were very significantly greater than the corresponding levels in the norepinephrine treated group (Figs. 1 and 2). The systemic excess lactate values were significantly less in the isoproterenol group than the norepinephrine group at each hour of therapy (Fig. 3), and the oxygen consumption was significantly greater in the former than the latter at all times after the first hour of treatment (Fig. 4). It should be noted that one dog (Table I, No. C4) failed to show the marked increases in cardiac output and stroke volume exhibited by the group as a whole and in this dog alone the systemic excess lactate did not decline.

Two dogs after receiving isoproterenol for the initial 2 and 3 hours of treatment were then administered norepinephrine instead for ½ and 1 hour, respectively. In both instances, the cardiac output and stroke volume dropped to the preisoproterenol shock levels (Table I, Nos. C6 and C7) and systemic excess lactate rose significantly (Fig. 3). Stroke work immediately before and ½ hour after changing therapy was calculated in these two dogs and in two of the four dogs of Group B initially treated with norepinephrine and subsequently with isoproterenol. These values are plotted graphically against the measured left ventricular end-diastolic pressure in Fig. 5. In each instance more stroke work was being done at a lower left ventricular end-diastolic pressure during isoproterenol therapy than during norepinephrine therapy, indicating the greater inotropic effects of isoproterenol.

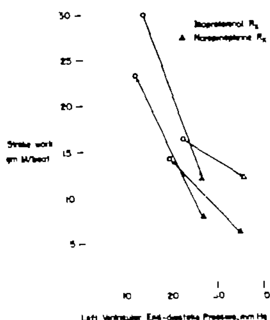


Fig. 5 Plot of stroke work (ordinate) versus left ventricular end-diastolic pressure (abscissa) in four shocked dogs during infusion of either norepinephrine (open triangles) or isoproterenol (open circles) and one half hour after changing the infusion to the opposite drug. In each instance, the greater stroke work done at lower LVEDP during isoproterenol infusion indicates the greater inotropic effect of this drug.

Early deaths As stated 14 dogs died before 15 minutes of shock had elapsed In five ventricular fibrillation occurred and in three asystole with pulselessness unresponsive to endocardial pacing The remaining six dogs showed progressive hypotension to the point of pulselessness despite a continuing sinus or nodal rhythm In three of these dogs, isoproterenol and external massage failed to return hemodynamic function and in two others, norepinephrine and massage similarly failed

Incomplete hemodynamic depression In seven dogs the embolization procedure was terminated before the cardiac output and stroke volume had been reduced by 50 per cent or before the mean aortic blood pressure had dropped below 90 mm Hg Four of these dogs were treated with isoproterenol two with norepinephrine and one served as control The responses to treatment were similar to the responses seen in dogs with more severe depression.

Myocardial metabolism in embolized dogs Data for calculation of per cent myocardial extraction of lactate pyruvate and oxygen were obtained after 15 minutes of shock and at 1 hour intervals thereafter in five dogs initially treated with isoproterenol in four dogs acting as controls, and in two dogs initially treated with norepinephrine (Table II) In all instances except one (B5) the per cent extractions of lactate and pyruvate 15 minutes after development of shock were considerably reduced below the pre-embolization levels seen in another group of 16 dogs also treated with propranolol before coronary embolization where lactate and pyruvate extraction averaged 30 ± 9 per cent and 35 ± 13 per cent, respectively In each instance isoproterenol therapy was associated with a decrease in the per cent extraction of oxygen and pyruvate The lactate extraction was variably affected in some instances increasing Norepinephrine treatment never lowered the oxygen extraction usually increased it above the levels noted after 15 minutes of shock and always increased it above the levels associated with isoproterenol therapy Pyruvate extraction decreased during norepinephrine therapy and lactate extraction was variably affected In only one control dog were these data available at the 1 hour interval when pyruvate and oxygen extraction were unchanged compared to the levels at 15 minutes after the development of shock and lactate extraction was slightly increased

Endocardial pacing Endocardial pacing was necessary in six dogs, three of which were in the control Group A and three in the isoproterenol Group C In two control dogs, right ventricular pacing was initiated because of progressive atrioventricular block In the third the right atrium was paced because of sinus bradycardia persisting despite intravenous atropine In two of the isoproterenol treated dogs, right atrial pacing was performed because of sinus arrest and nodal bradycardia in one of these *normal sinus rhythm returned* a few minutes after starting isoproterenol In the third isoproterenol treated dog right ventricular pacing was necessary because of atrioventricular block. After one hour of isoproterenol therapy normal sinus rhythm returned

pranolol levels in two nonembolized dogs one of which had received propranolol at the same dose used in the embolized dogs and the other of which had received a similar loading dose followed by an infusion of twice the amount of propranolol used in the embolized dogs. The higher infusion rate was used in the latter nonembolized dog to account for delayed metabolism of propranolol that might be present in a shocked animal The low doses of isoproterenol that would increase contractility above prepropranolol levels (Table IV) attests to the minimal degree of persisting propranolol induced depression of contractility

Lidocaine at 2 0 mg per minute caused no significant changes in stroke volume heart rate left ventricular systolic and end diastolic pressures or rate of rise of left ventricular pressure in the two dogs in which it effects were evaluated

Discussion

Rationale for the use of isoproterenol pure β-adrenergic receptor stimulating agent with marked inotropic and mild vasodilating properties, in the therapy of shock due to coronary occlusion (coronary shock) is predicated upon the concept that the primary cause of the severely reduced cardiac output in this situation is the diminished pumping ability of the heart the influence of peripheral vascular mechanisms being of secondary importance It is clear from the present data that in experimental coronary shock as induced in these experiments an increase in myocardial contractility effected by isoproterenol does result in substantial increases in cardiac output and in more adequate tissue perfusion (the latter reflected by decreases in systemic excess lactate) It should be pointed out that the doses of isoproterenol necessary to achieve these responses were large and on a per kilogram of body weight basis considerably greater than the amounts commonly used in man to treat complete heart block. These results are in marked contrast to the effects of norepinephrine in this situation While norepinephrine therapy did result in significant increases in blood pressure and systemic vascular resistance in shocked dogs and did prevent the high incidence of early death seen in the control group its continued administration was associated with continuing or increasing systemic excess lacticacidemia and no significant increase in cardiac output above the pretreatment level The greater increases in cardiac output and stroke volume effected in coronary shock in this study by isoproterenol than by a sympathomimetic agent with α and β adrenergic stimulating properties are in agreement with the findings of Smith and associates[7] in the only clinical study of this nature reported to date. These investigators compared the effects of consecutive 45 minute infusions of isoproterenol and metaraminol (Aramine) in ten patients in coronary shock and noted increases in cardiac output and stroke volume in seven patients following isoproterenol but not following metaraminol

The lack of response to either isoproterenol or norepinephrine in those dogs which rapidly deteriorated within the first 15 minutes following coronary embolization should be noted It appears that some instances of rapidly progressive coronary shock are unresponsive to sympathomimetic stimulation regardless of type

Several theoretic objections to the use of isoproterenol in coronary shock have been expressed First it has been suggested that the increased myocardial oxygen requirements[29] associated with its use would not be met by an adequate increase in oxygen delivery through increased coronary blood flow It has been argued that the administration of a drug without vasoconstrictive properties and with vasodilating properties in a situation usually characterized by hypotension might fail to increase aortic blood pressure[7] thereby leading to diminished coronary blood flow[1] In these experiments, however as a consequence of marked increases in cardiac output, isoproterenol increased mean aortic pressure in coronary shock despite a decrease in peripheral vascular resistance Whether coronary blood flow was also increased in these dogs as it is in the normal dog or man given isoproterenol[30] cannot be stated with certainty without its measurement It appears however that any increase in oxygen requirements of the myocardium as a whole that probably occurred during

isoproterenol therapy were more than adequately met by augmented coronary blood flow as evidenced by the fact that myocardial oxygen extraction was consistently decreased by isoproterenol. Increases in coronary blood flow during isoproterenol therapy in the shocked dogs probably occurred not only as a result of increased coronary perfusion pressure but also as a consequence of isoproterenol-induced coronary vasodilatation.[22] On the other hand it is quite possible and indeed likely that the oxygen requirements of certain regions of the myocardium were inadequately met in some shocked dogs during isoproterenol infusion and that the oxygen extraction data for the myocardium as a whole failed to reveal this. Cohen and co-workers[27] have pointed out that during isoproterenol administration dilution of that coronary venous blood which drains ischemic myocardium by coronary venous blood draining regions whose oxygen needs have been exceeded by an augmented oxygen delivery effected through regional increases in coronary blood flow may give a total picture of decreased myocardial oxygen extraction. The measurements of myocardial extraction of lactate and pyruvate in these experiments do not resolve this problem as they are subject to the same phenomenon. It is of interest however that in three of five dogs which these measurements were made myocardial extraction of lactate was increased following the first hour of isoproterenol therapy. This response to isoproterenol shock dogs contrasts with that usually noted patients with angina pectoris[22] suggesting that the hemodynamic consequences of the drug may benefit the balance of oxygen supply to myocardial oxygen need coronary shock whereas they stress this balance in the patient with coronary artery disease in the absence of severe hemodynamic impairment. The fact that norepinephrine consistently increased myocardial oxygen extraction suggests that this mode of therapy in coronary shock unlike isoproterenol failed to meet the oxygen requirements of the myocardium a whole. Similar conclusions were reached by Cronin[23] who noted myocardial lactate production during norepinephrine infusion but not during isoproterenol infusion in dogs following coronary embolization.

A second objection to the use of isoproterenol in coronary shock is the increased likelihood of the development of fatal arrhythmias. Clearly isoproterenol augments both ventricular excitability and automaticity,[1] making the infarcted heart more susceptible to an arrhythmia. We have attempted to offset this propensity by the concomitant administration of lidocaine and in the present experiments this was successful. The need for its administration was clear in one dog which developed ventricular fibrillation minutes after lidocaine was discontinued. Excessive doses of isoproterenol producing unnecessary increases in cardiac output led to fatal ventricular fibrillation in a second dog despite concomitant lidocaine administration. While different studies have suggested variable degrees of depression of myocardial contractility associated with lidocaine[25,26] the doses necessary to suppress arrhythmias in these experiments had no obvious effect on the contractility of either a normal or depressed dog heart. It was clear during the performance of these experiments that with isoproterenol therapy monitoring of the cardiac rhythm was necessary with immediate titration of therapy to avoid fatal arrhythmias (e.g., either increased lidocaine or decreased isoproterenol or both when there was evidence of ventricular irritability).

Infusion of dextran or other blood volume expanders in coronary shock has had variable clinical results.[27] It has been reasoned that such therapy would lead to an increase in cardiac output through the Frank-Starling mechanism. In the present experiments, the limited data on the effect of dextran infusion which were obtained showed the following (1) in the absence of isoproterenol at the high left ventricular end-diastolic pressures which were present in the dogs following coronary embolization dextran infusion sufficient to further increase left ventricular end-diastolic pressure caused no increase in stroke volume; ( ) on the other hand with isoproterenol therapy and a result of lower left ventricular end-diastolic pressure dextran infusion sufficient to increase this pressure an amount similar to that effected in the

pranolol levels in two nonembolized dogs one of which had received propranolol at the same dose used in the embolized dogs and the other of which had received a similar loading dose followed by an infusion of twice the amount of propranolol used in the embolized dogs. The higher infusion rate was used in the latter nonembolized dog to account for delayed metabolism of propranolol that might be present in a shocked animal. The low doses of isoproterenol that would increase contractility above prepropranolol levels (Table IV) attests to the minimal degree of persisting propranolol induced depression of contractility.

Lidocaine at 2.0 mg. per minute caused no significant changes in stroke volume heart rate left ventricular systolic and end diastolic pressures or rate of rise of left ventricular pressure in the two dogs in which its effects were evaluated.

Discussion

Rationale for the use of isoproterenol a pure β-adrenergic receptor stimulating agent with marked inotropic and mild vasodilating properties in the therapy of shock due to coronary occlusion (coronary shock) is predicated upon the concept that the primary cause of the severely reduced cardiac output in this situation is the diminished pumping ability of the heart the influence of peripheral vascular mechanisms being of secondary importance.[1] It is clear from the present data that in experimental coronary shock as induced in these experiments, an increase in myocardial contractility effected by isoproterenol does result in substantial increases in cardiac output and in more adequate tissue perfusion (the latter reflected by decreases in systemic excess lactate). It should be pointed out that the doses of isoproterenol necessary to achieve these responses were large and on a per kilogram of body weight basis considerably greater than the amounts commonly used in man to treat complete heart block. These results are in marked contrast to the effects of norepinephrine in this situation. While norepinephrine therapy did result in significant increases in blood pressure and systemic vascular resistance in shocked dogs and did prevent the high incidence of early death seen in the control group its continued administration was associated with continuing or increasing systemic excess lacticacidemia and no significant increase in cardiac output above the pretreatment level. The greater increases in cardiac output and stroke volume effected in coronary shock in this study by isoproterenol than by a sympathomimetic agent with α and β-adrenergic stimulating properties are in agreement with the findings of Smith and associates in the only clinical study of this nature reported to date. These investigators compared the effects of consecutive 45 minute infusions of isoproterenol and metaraminol (Aramine) in ten patients in coronary shock and noted increases in cardiac output and stroke volume in seven patients following isoproterenol but not following metaraminol.

The lack of response to either isoproterenol or norepinephrine in those dogs which rapidly deteriorated within the first 15 minutes following coronary embolization should be noted. It appears that some instances of rapidly progressive coronary shock are unresponsive to sympathomimetic stimulation regardless of type.

Several theoretic objections to the use of isoproterenol in coronary shock have been expressed. First it has been suggested that the increased myocardial oxygen requirements[30] associated with its use would not be met by an adequate increase in oxygen delivery through increased coronary blood flow. It has been argued that the administration of a drug without vasoconstrictive properties and with vasodilating properties in a situation usually characterized by hypotension might fail to increase aortic blood pressure,[7] thereby leading to diminished coronary blood flow. In these experiments, however, as a consequence of marked increases in cardiac output isoproterenol increased mean aortic pressure in coronary shock despite a decrease in peripheral vascular resistance. Whether coronary blood flow was also increased in these dogs as it is in the normal dog or man given isoproterenol[30] cannot be stated with certainty without its measurement. It appears however that any increase in oxygen requirements of the myocardium as a whole that probably occurred during

could not be excluded When shocked dogs initially treated with norepinephrine were given isoproterenol, hemodynamic function and tissue perfusion were significantly improved when shocked dogs initially treated with isoproterenol were then given norepinephrine hemodynamic function and tissue perfusion worsened Dextran infusion in shocked dogs sufficient to increase left ventricular end-diastolic pressure increased cardiac output only when isoproterenol was being given Generally similar responses to norepinephrine and isoproterenol therapy were seen in a group of dogs with less severe hemodynamic depression following coronary embolization.

From these stud es it is concluded that isoproterenol infusion concomitant with continuous lidocaine nfusion and intermittent expansion of blood volume merits clinical evaluation in the therapy of shock due to myocardial infarction

Sincere appreciation is extended to Dr A. V N Goodyer Professor of Medicine, ithout hose support nd ad ice these studies ould not hav been completed The expert technical assistance of Miss Carol Maka and Miss Frances Korb is acknowledged with pleasure

REFERENCES

1 Gunnar R M Cruz, A Boswell, J Co, B S Pietras, R J and Tobin, J R. Myocardial infarction ith shock Hemodynamic studies and results of therapy Circulation 23 753 1966
2. Binder M J Effect of vasopressor drugs on circulatory dynamics in shock following myocardial infarction Am. J Cardiol. 16:834 1965
3 Smulyan, H Cuddy R P and Eich, R. H. Hemodynamic effects of pressor agents in septic and myocardial infarction shock, J A M A 190 188, 1964
4 Binder M J Ry n, J V, J Marcus, S., Mugler F J Strange, D and Agress, C. M Evaluation of therapy in shock following acute myocardial infarction, Am. J Med. 18:622, 1955
5 Binder M J The mechanism and treatment of shock in acute myocardial infarction, Progr Cardiovas. Dis. 1:206, 1958
6 Cronin, R F P Moore S nd Marpole D C. Shock following m ocardial infarction. A clinical survey of 140 ases, Canad M A J 93:57 1965
7 Smith, H J Oriol, A March, J nd M Gregor M Hemod namic studies in cardiogenic shock Tre men w h isoproterenol and metaraminol, Circula ion 35 1084, 1967
8 Freis, E. D Schnaper H W Johnson, R. L and Schreiner G E. Hemodynamic alterations in acute myocardial infarction. I Cardiac output, mean arterial pressure, total peripheral resistance, central" and total blood volumes, venous pressure, and a erage circulation time, J Clin. I vest. 31:131 1952.
9 Gilbert, R. P Goldberg M and Griffin, J Circulatory changes in acute myocardial infarction, Circulation 9:847 1954
10. Smith W W Wikler N S and Fox, A. C. Hemodynamic studies of patients w th myocardial infarction, Circulation 9:352, 1954
11 Gammill, J F Applegarth, J J Reed, C. E., Fernald, J D and A tenucci, A. J Hemodynamic changes following acute myocardial infarction using the dye injection method for cardiac output determination, Ann. I t. Med. 43 100, 1955
12. Goodyer A. V N Huvos, A., Eckhardt, W F and Ostberg R. H Thermal dilution curves in the intact animal, Circulation Res. 7:432, 1959
13. Goodyer A. V N Goodkind, M J and Landry A B The ventricular response to pressur load Left ventricular function curves in intact animals, Circulation Res. 10:885 1962.
14 Evonuk, E Imig C. J Greenfield, W and Eckstein, J W Cardiac output measured by thermal dilution of room temperature saline J Appl Physiol 16:271 1961
15 Huckabee W E. Control of concentration gradients of pyruvate and lactate across cell membranes in blood, J Appl Physiol. 9 163 1955
16 Fearon, R E Propranolol in the prevention of ventricular fibrillation due t experimental coronary artery occlusion ith observations on its mode of action, Am J Cardiol 20:222 1967
17 Jacobey J A T ylor W J Smith, G. T Gorlin, R and Harken, D E A new therapeutic pproach to acute coronary occlusion I Production of standardized coronary occlusion with microspheres, Am J Cardiol 9:60 1962
18. Boyer N H Medical progress Cardiogenic shock, New England J Med 230:226, 1944
19 Fearon R E Coronary shock, Conn Med 31:609 1967
20 Krasnow N Rolett, E L Yurchak, P M Hood, W B J and Gorlin, R. Isoproterenol and cardiovascular performance Am J Med 37:514 1964
21 Klocke F J Kaiser G A Ross, J J and Braunwald, E An intrinsic adrenergic vasodilator mechanism in the coronary vascular bed of the dog, Circulation Res. 16:376, 1965
22. Cohen, L S Elliott, W C Klein, M D and Gorlin, R Coronary heart disease Clinical cinearteriograp hic and met bolic correlations, Am. J Cardiol 1 153 1966
23 Cronin, R F P Effect of isoproterenol nd norepinephrine on m ardial function in experimental cardiogenic shock Am Hr rt J 4:387 1967
24 Hoffman, B F nd Cranefield, P F Ph siological basis of ardiac arrh hmias, Am J Med 37:670, 1964
25. Austen, W G., and Moran, J M Cardiac and

peripher l asc lar fect of lidocaine and proc inamide Am J Cardiol 16:701 1965
26 Harrison, D C Sprouse J H nd Morrow A G The anti-arrh thmic properties of lidocaine nd procaine amide, Circulation 28:486 1963
7 C b J N Luna M H Daddario, R C nd I st I F Studies n clinical shock and hypotension A Hemodynamic effect of dextran, Circulation 35:316, 1967
28 Epstein F H nd Relman A. S. Transfusion treatment of shock due to myocardial infarction New England J Med 241:889 1949
29 Cronin, R. F I Hemodynamic and metabolic effects of beta-adrenergic blockade in exercising dogs, J Appl. Physiol. 22:211 1967

Stress distribution within the left ventricular wall approximated as a thick ellipsoidal shell

Alan Y. K. Wong, Ph.D.
P. M. Rautaharju, M.D., Ph.D.
Halifax, Nova Scotia, Canada

In 1805 Laplace[1] derived an equation that later became known as the Law of Laplace. The equation was derived for treatment of capillary action and it relates the pressure difference across the surface to its curvature and the surface tension. Mathematically, the Law of Laplace is expressed as

$$P = t\left(\frac{1}{r} + \frac{1}{R}\right) \qquad (1)$$

where P is the pressure difference across the surface, t is the wall tension, r and R are the principal radii of curvature.

Application of the Law of Laplace to the heart originated through the work of Woods[2] in 1892 and more recently through the articles of Burton. These two investigators among a few others have pointed out that the size and the shape of the left ventricle greatly affect its performance as a pump.

There is presently a great deal of confusion when attempts have been made to use the Law of Laplace to study the behavior of the left ventricle. One of the main reasons for the confusion would seem to be that the tension as defined by Laplace for a thin-walled structure becomes an ill-defined and practically meaningless quantity in a structure with a thick wall. Formulas which are more complex than the beautifully simple Law of Laplace are necessary for computation of the stress in the wall of the left ventricle. The added complexity, however, is no longer a serious obstacle now that modern electronic computer techniques are increasingly available to most medical investigators.

The studies of Rushmer and Thal, Ninomiya and Wilson, and Hawthorne indicate that the wall of the left ventricle at end-diastole is best described as a thick-walled ellipsoid of revolution. Mathematical equations for calculating the stress distribution across the wall of such a structure have not yet been derived, as was recently pointed out by Hawthorne and Sandler and Dodge. The main purpose of the present investigation was to formulate these necessary equations and to utilize them to determine the stress distribution in a thick-walled left ventricle in conditions simulating hypertrophy, dilatation, and hypertension.

Methods

Assumptions and approximations. The six assumptions listed below are made to

From the Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada.
This work has been supported through the research grants from the Medical Research Council of Canada and the Canadian Heart Foundation.
Received for publication on Aug. 7, 1967.

simplify the formulations and derivations needed for construction of the model.

1. The left ventricle is considered as a thick ellipsoidal shell with two equal minor semiaxes.

2. The myocardium is assumed to be an elastic, isotropic, and homogeneous material which will completely recover its original form when the distorting forces are removed. Thus the myocardium is assumed to obey Hooke's Law, which can be expressed in tensor form

$$\epsilon_{ij} = \frac{1+\mu}{E}\sigma_{ij} - \frac{\mu}{E}\delta_{ij}\sigma_{kk} \qquad (2)$$

where μ = Poisson's ratio, E = Young's Modulus, δ_{ij} = Kronecker delta, ϵ_{ij} = strain tensor, σ_{ij} = stress tensor, and σ_{kk} = diagonal stress tensor.

3. The myocardial distortion due to the applied force is a purely radial displacement (along the radius of curvature) and the intraventricular pressure acting normal to the surface is the only load on the heart.

4. Wall forces such as bending moments and shears are neglected because of the symmetry of the chosen configuration.

5. It is assumed that the heart is supported by surrounding tissues and the forces due to the inertia of the heart muscle and the blood are not considered.

6. The heart wall is in a state of equilibrium and is acted upon by the following stresses: (i) the radial stress σ_{RR} which acts normal to the surface and is balanced by (ii) the radial components of the longitudinal stress $\sigma_{\phi\phi}$ and the latitudinal stress $\sigma_{\theta\theta}$ acting within the wall.

The geometry of the ellipsoidal left ventricle. Generally, it can be said that the inner and the outer surface of the left ventricle is obtained by rotating a plain curve about an axis in its plane. When the *ellipsoidal approximation is used*, these surfaces are generated by rotating a semiellipse about its major axis.

As shown in Fig. 1, the configuration of the ellipsoidal ventricle is determined by the semimajor axis OA and the semiminor axis, OB. The contour at any point P on the *endocardial surface* of the ellipsoidal ventricle is given by the principal radii of curvature r and R. The values for r and R can be calculated at any level between the apex and the base of the heart from the angle ϕ between the semimajor axis OA and R or r (pointing to P at the endocardial surface). These radii of curvature are related to each other by the following expression:

$$r = (1 + \lambda \operatorname{Sin} \phi)\, R$$

where λ is a parameter which is less than 1. As shown in Fig. 1, the circles described by R *and r are in* the planes which are mutually perpendicular to each other.

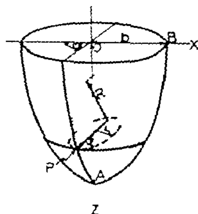


Fig. 1. The contour at any point P at the endocardial surface of the ellipsoidal ventricle is given by the principal radii of curvature r and R. The configuration of the ventricle is determined by the semimajor [illegible] (OA) and the semiminor axis b (OB). The values for r and R can be calculated at any level between the apex and the base of the heart from the angle ϕ between the semimajor axis OA and the normal drawn to the endocardial surface at P.

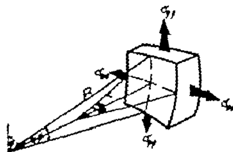


Fig. 2. Shell element which is cut from the [illegible] tricular wall when the principal radii of curvature [illegible] and R trace through the [illegible] through a [illegible] infinitely small angle $d\phi$ and $d\theta$ respectiv[illegible] ly.

Notice that r is not identical to the radius of the parallel circle except at the equator

Stress in a shell element. A shell element (Fig 2) is cut by r and R when they each trace across the wall through an infinitely small angle $d\phi$ and $d\theta$ respectively. The arc lengths of this element are described by $Rd\phi$ and $rd\theta$

When subjected to the radial, the latitudinal and the longitudinal stresses, the shell element will be distorted by a displacement u which is a function of R only. From Equation (2) the stresses are related to the strains l_{RR}, $l_{\theta\theta}$, $l_{\phi\phi}$ by the following equations

$$\frac{du}{dR} = l_{RR} = \frac{1}{E}(\sigma_{RR} - \mu(\sigma_{\theta\theta} + \sigma_{\phi\phi})) \quad (3)$$

$$\frac{u}{r} = l_{\theta\theta} = \frac{1}{E}(\sigma_{\theta\theta} - \mu(\sigma_{RR} + \sigma_{\phi\phi})) \quad (4)$$

and

$$\frac{u}{R} = l_{\phi\phi} = \frac{1}{E}(\sigma_{\phi\phi} - \mu(\sigma_{RR} + \sigma_{\theta\theta})) \quad (5)$$

where σ_{RR}, $\sigma_{\theta\theta}$, $\sigma_{\phi\phi}$ and u are functions of R only

A volume element shown in Fig 3 is subjected to the radial, the latitudinal and the longitudinal stresses. The lengths of the edges of this element are dR, $rd\theta$ and $Rd\phi$. As indicated in Fig 3 the forces acting on the shell element are

i. The longitudinal force $F_{\phi\phi}$, i.e. the force in the direction of the meridian, is equal to the longitudinal stress × the area on which it is acting ($F_{\phi\phi} = \sigma_{\phi\phi}$ rdRdθ)

The radial component and the tangential components of this force are $F_{\phi\phi}$ Sin $(\frac{d\phi}{2})$ and $F_{\phi\phi}$ Cos $(\frac{d\phi}{2})$ respectively. Since there are two longitudinal forces acting in opposite directions the tangential components cancel each other; the net force is therefore a radial force of magnitude $2F_{\phi\phi}$ Sin $(\frac{d\phi}{2})$ pointing toward the axis of rotation

ii. The latitudinal or loop forces $F_{\theta\theta}$ act in the direction of the parallel circles. They also contribute two radial components, $F_{\theta\theta}$ Sin $(\frac{d\theta}{2})$

iii. Two forces are acting radially, one is $\sigma_{RR}rRd\theta d\phi$ pointing inward, the other is $(\sigma_{RR}rR + \frac{d}{dR}(\sigma_{RR}rR)dR)d\theta d\phi$ pointing outward. The resultant of these forces $\frac{d}{dR}(\sigma_{RR}rR)dRd\theta d\phi$ (i.e. dF_{RR}) is thus pointing in the outward direction

As the shell element is in equilibrium the sum of the radial components of $F_{\phi\phi}$ and $F_{\theta\theta}$ will be equal to the net radial force dF_{RR}. Hence,

$$2F_{\phi\phi}\,\mathrm{Sin}\left(\frac{d\phi}{2}\right) + 2F_{\theta\theta}\,\mathrm{Sin}\left(\frac{d\theta}{2}\right) = dF_{RR}$$

For a very small angle

$$\mathrm{Sin}\ X \simeq X$$

For an equilibrium condition

$$\frac{d}{dR}(\sigma_{RR}rR) - R\sigma_{\theta\theta} - r\sigma_{\phi\phi} = 0. \quad (6)$$

Equation (6) together with Equations (3), (4) and (5) is adequate for the solution of σ_{RR}, $\sigma_{\phi\phi}$ and $\sigma_{\theta\theta}$.

The solution of equations. The Appendix shows that the expressions for the radial, the longitudinal and the latitudinal stresses take the following forms if an internal pressure P is acting on the inner surface of the chamber while the pressure at the outer ventricular surface is assumed to be zero

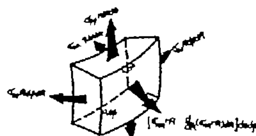


Fig. 3. The volume element is subjected to the radial, latitudinal, and longitudinal stress components.

$$\sigma = \frac{PR}{(R + T) - R^{n}} R \left(1 - \frac{(R + T)}{R^{n}}\right) \qquad (7)$$

$$= \frac{1}{C + \frac{1}{k}} \frac{PR}{(R + T) - R^{n}} R \left(\left(\frac{n + 1}{2} - C\right) + \frac{\left(C - \frac{1 - n}{2}\right)(R + T)}{R^{n}}\right) \qquad (8)$$

and

$$\sigma_{\phi\phi} = \frac{1}{C + \frac{1}{k}} \frac{PR_{o}}{(R + T) - R^{n}} R \left(\left(C \frac{n + 1}{2} + \frac{C}{k}\right) - \left(C \frac{1 - n}{2} + \frac{C}{k}\right) \frac{(R + T)}{R^{n}}\right) \qquad (9)$$

where

$$n = \frac{4k\mu (1 - k) + (1 - \mu)(4 + 5k)}{k^{2}(1 - \mu)} \qquad k = 1 + \lambda \mathrm{Sin}\, \phi$$

$$L = \frac{k + \mu}{1 + k} \qquad C = \frac{\mu (1 - k)}{1 + k\mu}$$

R is the endocardial radius of curvature (i.e. radius of curvature at the endocardial surface) of the meridian for a certain constant value of ϕ. T is the thickness of the heart wall.

The relationship between the radii of curvature R and r at the endocardial surface is

$$r = kR_{m}$$

and

$$R = \frac{R}{(1 + \lambda \mathrm{Sin}\, \phi)} \qquad r = \frac{R}{(1 + \lambda \mathrm{Sin}^{2}\phi)}$$

The parameter R_1 is equal to the value of the radius of curvature for $\phi = 0$, i.e. for the vertex of the shell. For a spherical shell in which $\lambda = 0$ and $k = 1$, the parameter n is 3. The radial, the longitudinal, and the latitudinal stresses are

$$\sigma_{R} = \frac{PR_{o}}{(R_{o} + T) - R_{o}^{3}} \left(1 - \left(\frac{R_{o} + T}{R}\right)\right) \qquad (10)$$

and

$$\sigma = \sigma_{\phi\phi} = \frac{PR_{o}^{3}}{(R_{o} + T) - R_{o}^{3}} \left(1 + \frac{1}{2}\left(\frac{R_{o} + T}{R}\right)\right) \qquad (11)$$

Equations (7), (8), and (9) give the variation of stresses within the heart wall. At the endocardial surface R is equal to R_m and the radial as well as the latitudinal and the longitudinal stresses will be maximum. The stress progressively decreases toward the outer portion of the wall. At the epicardium the radial stress is zero while the tensile stresses (i.e. the latitudinal and longitudinal stresses) are minimal.

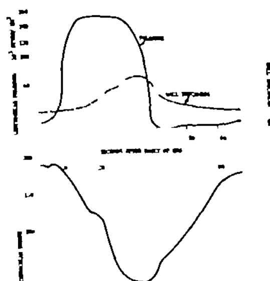


Fig 4 Time course of ventricular pressure wall thickness and ventricular volume The curves are reconstructed from angiocardiographic data published by Sandler and Dodge, Circulation Res. 13 104 1963 (with permission from the authors and the American Heart Association, Inc)

Results

For the computation of the radial the latitudinal and the longitudinal stresses as given by Equations (7) (8) and (9) a record of the pressure the volume and the wall thickness is needed However such data are not available from normal people because of the risks involved in the procedure Fig 4 shows the time course of pressure volume and wall thickness during contraction of the left ventricle of a patient who had rheumatic heart disease, mitral insufficiency and mitral stenosis. These curves are reconstructed from the data given by Sandler and Dodge Despite the diseased condition these curves will be used here arbitrarily as normal reference curves. This is quite arbitrary but acceptable because the purpose here is to evaluate the relative change stress distribution with either pressure or volume changes simulating conditions such as hypertension and dilatation

Stress profile in the heart wall As the myocardium is assumed to be an isotropic and homogeneous elastic medium theoretically the radial stress decreases from maximum i e at the endocardium to zero at the epicardium. This is illustrated by Fig 5 which shows the computed radial stress at the equator and the apex of the ellipsoidal ventricle The profiles of the radial stress for sections between the apex and the equator would lie between the curves plotted in Fig 5

Corresponding to the radial stress distribution are two tensile stress components, the latitudinal and the longitudinal stresses. These stress profiles as shown in Fig 5 were computed with the same parameters as the radial stress.

It is noted that the magnitude of the latitudinal stress is almost twice that of the corresponding longitudinal stress. One interesting feature is that while the radial stress decreases to zero at the epicardium there is always a finite amount of tensile stress at the outermost layer unless the transmural pressure is zero.

Time course of tensile stresses on the endocardium The time course of the tensile stress at the endocardium is shown in Fig 6 computed from the time point 0 01 second after the onset of QRS until the end of the systole In this 3 dimensional display the heaviest line represents the time course of the stress at the apex. The last curve with the highest magnitude is the stress acting on the base and in between are the corresponding curves for five intermediate regions of the heart between the apex and the base

The stress rises rapidly during the pre ejection phase and reaches a maximum during the isovolumetric contraction. At the apex, the latitudinal and the longitudinal stresses are equal whereas in other parts of the heart the latitudinal stress increases proportionately more than the longitudinal stress.

Longitudinal and latitudinal stresses as functions of radius of curvature The longitudinal ($\sigma_{\theta\theta}$) and the latitudinal ($\sigma_{\phi\phi}$) stresses are plotted as a function of the radius of curvature R in Fig 7 Here the left ventricle is assumed to be an ellipsoidal thick shell with uniform wall thickness. The semimajor and the semiminor axis of the ellipsoid are a and b respectively In the present study the ratio of a to b is taken as R is the radius of curvature at the apex and is equal to b^2 a

The solid line is the latitudinal stress and the broken line refers to the longitudinal

stress. The radius of curvature R on the abscissa is expressed in multiples of R_1 the magnitude of which in turn depends on the configuration and the volume of the ellipsoidal heart.

It is noted that at any certain volume and configuration the stresses in the wall of the ellipsoidal heart do not increase linearly with the radius of curvature. Generally speaking, doubling of R will increase the latitudinal stress about 1.5 times and the longitudinal stress by a factor of 1.2 and the increase in the longitudinal stress can be practically negligible at the almost horizontal portion of the curve.

Fig. 7, A and C displays the computed results from studies of the effect of dilatation and variations of the shape of the ventricular cavity on the stress distribution in the heart wall. It is emphasized that the results presented here were obtained through computer simulation. The stress distributions in these different conditions are given as relative values with respect to reference values shown in Fig. 7, B.

In Fig. 7, C, R_1 is the radius of curvature at the apex of an ellipsoidal heart with a volume of 215 c.c., i.e., a 40 per cent increase from the reference condition. R_1 is equal to 1.5 R. The stresses on the myocardium in such a dilated heart are slightly increased at portions where the radius of curvature is large, for instance at the equator.

The radius of curvature at various parts of the heart is described by

$$R = \frac{R_1}{(1 + \lambda \text{Sin}\, \phi)}$$

where ϕ is the angle between R and the axis of the heart.

The variation of R from the apex to the base depends on the factor

$$k = (1 + \lambda Sin\, \phi)$$

At the apex $\phi = 0$ and $R = R_1$, and R is equal to 8R at the base where $\phi = \pi/2$. In the above diagram the abscissas vary from $1R_1$ to $8R_1$, which is the range of radius of curvature of the heart. Besides relating the stresses with the linear dimensions of the heart, Fig. 7 also describes the stress distribution from

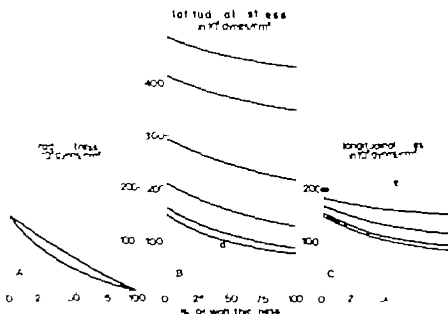


Fig. 5. Distribution of radial, latitudinal, and longitudinal stress from endocardium (0 per cent) to epicardium (100 per cent) in the wall of ellipsoidal ventricle. The curves show the stress profiles at the equatorial (e) and apical ( ) cross sections and at five intermediate sections between apex and equator. The lines are computed for an intraventricular pressure of 144 × 10³ dynes per square centimeter, wall thickness of 0.73 cm., and the ratio of major axis to minor axis = 2.

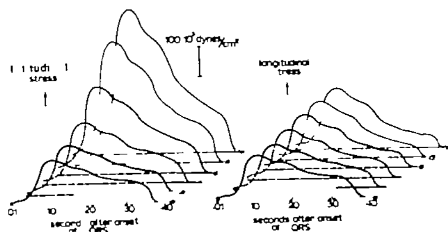


Fig 6 Time course of endocardial latitudinal and longitudinal tress The numbers 0 t 10 indicat the stress curves t various regions from the pex (0) to the base (10) of the left entricle

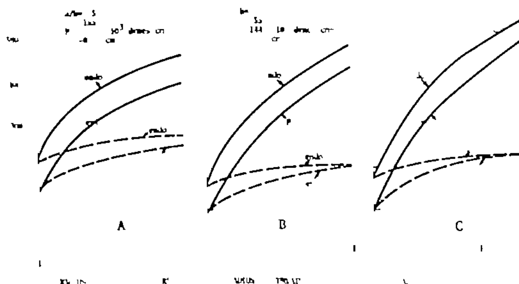


Fig 7 Distribution of latitudinal (solid lines) and longitudinal (broken lines) stress t the endocardium (*endo*) nd the epicardium (*p*) as functions of radius of curv ture (*R*) R is computed from the equation

$$R = \frac{R}{\left(1 - 0.75 \sin \frac{2}{20}\right)}$$

R′ R and *R″* are the adii of curv ture the pex in nearly spherical entricle (*A*), in normal heart (*B*) and in simulated dilated heart (*C*) These curves also indicate the stress distribution from the apex (*R* = *R*) t the base here *R* 3*R*

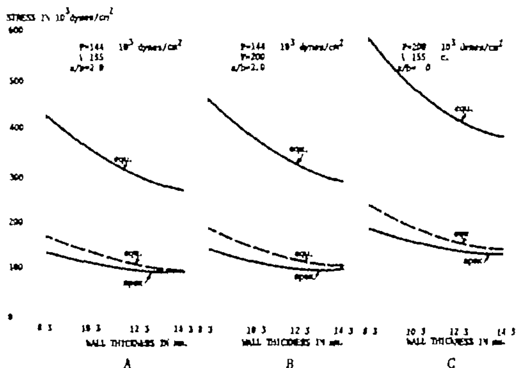


Fig. Latitudinal (solid lines) and the longitudinal (broken lines) tress in the heart wall as function of th kness. Curves labelled equ. and apex are stress t the equator and apex of the ellipsoidal entricle (A), ference normal heart (B), dilated heart ith normal pressure (C), reference normal heart with increased entric lar pressure

Table I. Wall stress in simulated dilatation and hypertrophy at the end of isovolumetric contraction

	Reference normal	*Simulated hypertrophy*	*Simulated dilated*
Ventricular volume (c.c.) at the onset of ejection	155	155	200
Pressure 10^3 dynes/cm	144	200	144
Wall thickness (cm.)	0.83	1.19	0.89
Latitudinal stress at equator 10^3 dynes/cm.	435	435	435
Longitudinal stress at equator in 10^3 dynes/cm	176	170	177
Latitudinal and longitudinal stress at apex in 10 dynes/cm	136	150	138

the apex to the base of the ellipsoidal heart.

Relations of the stresses and the wall thickness. In Fig. 8 the stresses at the equator and at the apex are plotted versus the wall thickness. For the purpose of clarity only the stresses acting on the endocardium are presented. As the radii of curvature at the apex are the same, the latitudinal and the longitudinal stresses at this part of the heart are equal. Hence the two curves at the apex coincide in the diagram.

According to the model used, an increase of the wall thickness actually decreases the force per unit area necessary to maintain the same pressure. It is seen that at a pressure of 144 × 10 dynes per square

centimeter (110 mm Hg) and a volume of 155 c.c. (at the onset of the ejection period referring to Fig 4) the maximum stress developed is 430 × 10 dynes per square centimeter at a wall thickness of 0.83 cm When the wall thickness increases to 1 43 cm the stress needed to maintain the same pressure declines to 267 × 10³ dynes per square centimeter

Fig 8 B and C has the same features displayed as in Fig 8,A except that in Fig 8,B the olume is ncreased to 200 c.c and in Fig 8 C the pressure is elevated to 200 × 10³ dynes per square centimeter (154 mm Hg) An ncreased pressure load elevates the stresses more than an increased volume load

It could be speculated that hypertrophy is an adaptive mechanism which acts to keep the wall stress constant despite dilatation or hypertension To examine this postulate in more detail the reference normal' heart was compared with the dilated and the h pertensive heart to determine how much hypertrophy (increase in the wall th ckness) is required to keep the latitud nal stress at the equator constant. The results are given n Table I It is seen that a very small ncrease n the wall thickness (0 6 n m) is enough to ma nta n the stress const nt when the end-diastolic volume s ncreased from 155 to 200 c c A 3 6 n m increase of th wall thickness is requ red to keep the stress unchanged when the pressure is increased from 110 to 154 n m Hg It must be noted however that an ncrease of the wall thickness by 0 6 mm when the volume of the ventricle ncreases from 150 to 200 c.c impl es a ?7 per cent ncrease of the mass of the left ventricle

Discussion

Formal analysis of the stress distribution with n the myoc rd um has not been previously reported the l terature However Kreuzer and Schoeppe measured the intramyocard al pressure t arious layers of the m rd um Their result showed that i a d ad he rt th pressure decreases a nc l n ar fashion from the endocardium to the epicard um The mag n tude of the tr myocardial pressure varied from the pex to the base depending on the position. During sy tole in a normal beating heart the intramyocardial pressure decreased towards the more superficial layers of the myocardium, but the maximum ntramyocardial pressure exceeded the maximum intraventricular pressure in an inner layer near the endocardial portion of the ventricular wall.[9]

Recently Sonnenblick and associates[a] related the left ventricular filling and the sarcomere length of the heart muscle fibers in dogs. Their study showed that at a given ventricular filling pressure the sarcomeres are longest in the inner layers of the left ventricular wall decreasing in length towards the more superficial layers As the authors suggest this would indicate that the stress is maximum at the endocardium and minimum at the epicardium

The radial stress distribution within the myocardium as computed in this study resembles the ntramyocardial pressure distribution in a dead heart as illustrated by Kreuzer and Schoeppe The latitudinal and the longitudinal stresses also beha e as implied by the results of Sonnenblick and associates. It can be speculated that in a dead heart or in a heart at a passive state the myocardium behaves like an isotropic homogeneous elastic medium

A quantitative analysis and a discussion of the functional aspects of the cardiac hypertrophy has been reported notably by Linzbach and ts biological significance was discussed in detail by Badeer[11] Whether "physiologic or pathologic hypertrophy is generally considered as an adaptive mechanism. For example a moderate physiologic hypertrophy arises as a result of cardiac dilatation This often occurs in athletes or laborers whose strenuous exertion demands greater cardiac output Extensive hypertrophy n m ny occasions is a result of an increase of pressur load such as valvular stenosis or arterial hypertension.

Although histologic hanges n h pertrophied fibers ha been reported[13] the functional aspect of h pertrophy re still speculati Some in estig tors ha e noted a greater cont acting forc developed b hypertrophied fibers, or an mprovement in the work capacit of the heart while others found neither ny changes n resting or contractile tension, nor any biochemical

differences between the hypertrophied muscle (rat papillary muscle) and the normal heart.[1]

The calculations made by Sandler and Dodge[7] based on the Law of Laplace, showed no significant stress differences between hypertrophied hearts and those with a normal wall thickness. Also Badeer[12] in applying the Law of Laplace to the heart suggested that the force per unit area in a hypertrophied heart tends to remain unchanged. The computed results in the present study support the conclusions of Badeer[12] and those presented by Sandler and Dodge.[7]

Although the model used here gives computed results in agreement with the observed intramyocardial pressure and the sarcomere length of the ventricular fibers during the passive state, it is very likely that the myocardium does not behave as a homogeneous and isotropic medium during ventricular contraction. This is evidenced by the discrepancy between the calculated radial stress and the observed intramyocardial pressure in the systolic phase.

Sonnenblick has demonstrated that from the point of view of the dynamics, the cardiac muscle fibers (cat papillary muscle) behave somewhat like the skeletal muscle fibers. In other words, the sliding filament model is probably valid also for the cardiac muscle. However, in the present work, no attempt has been made to develop a model at the molecular level.

Although the model presented here is more suitable than the Law of Laplace and may be adequate for description of the stress distribution in the heart wall during a passive state, more refined models should be sought for analysis of dynamic events and stress distribution during contraction of the heart muscle.

Summary

Tension as defined by the Law of Laplace for a thin wall is an ill-defined and practically meaningless quantity in a structure like the human left ventricle. To overcome the shortcomings of Laplace's formula, a formula is derived for the stress distribution within the myocardium which is assumed to be an isotropic, homogeneous elastic medium. This expression is generalized so that it is applicable for the left ventricle which is assumed as either a spherical thick shell or an ellipsoidal shell or a paraboloid of revolution. The formula can be used for any of the three configurations by varying certain parameters according to known or assumed dimensions of the heart. The patterns of stress distribution were computed for various phases of contraction of a simulated normal heart. The stress distributions were also determined at the end of the isovolumetric contraction in conditions simulating hypertrophy, dilatation, and hypertension. In an ellipsoidal structure the wall stress does not increase linearly with the radius of curvature. As a representative result, doubling of the radius of curvature will increase the latitudinal stress about 1.5 times and the longitudinal stress by a factor of 1.2. Although several simplifying assumptions were necessary to facilitate computing of the stress profiles, the results obtained are more realistic and accurate than can be expected from models which approximate the left ventricle as a sphere or a cylinder or a structure with a thin wall.

Appendix

Stress distribution in the thick-walled spherical, ellipsoidal or paraboloidal structure. Since the radial displacement u has been considered as a function of R only, the radius of curvature, a circle with a radius R or r has a radius (R + u) or (r + u) after strain. The fractional extensions of the circumference in longitudinal and latitudinal directions are given respectively by

$$l_{\phi\phi} = \frac{2\pi(R+u) - 2\pi R}{2\pi R} = \frac{u}{R}$$

and

$$l_{\theta\theta} = \frac{2\pi(r+u) - 2\pi r}{2\pi r} = \frac{u}{r}$$

The extension in a radial direction is simply the change of u with R. Hence the radial extension (l_{RR}) is

$$l_{RR} = \frac{du}{dR}$$

From the relationship between the strain

and the stress as given in Equation (2) the following equations are obtained

$$\frac{du}{dR} = l \quad = \frac{1}{E}(\sigma \quad - \mu(\sigma \quad + \sigma_{\phi\phi})) \quad (A1)$$

$$\frac{u}{R} = l_\theta \quad = \frac{1}{E}(\sigma_{\theta\theta} - \mu(\sigma_{\phi\phi} + \sigma \quad)) \quad (A2)$$

$$\frac{u}{R} = l_{\phi\phi} = \frac{1}{E}(\sigma_{\phi\phi} - \mu(\sigma \quad + \sigma_{\theta\theta})) \quad (A3)$$

The differential equation for equilibrium is

$$\frac{d}{dR}(\sigma \quad rR) - R\sigma_\theta \quad - r\,\sigma_{\phi\phi} = 0 \qquad (A4)$$

where σ_{RR} = radial stress, $\sigma_{\theta\theta}$ = latitudinal stress, and $\sigma_{\phi\phi}$ = longitudinal stress. The principal radii of the surface of revolution are

$$R = \frac{R}{(1 + \lambda \sin \phi)}$$

and

$$r = \frac{R}{(1 + \lambda \sin \phi)}$$

where R is the radius of curvature for $\phi = 0$ i.e at the vertex of the shell

R and r are hence linked by equation

$$r = (1 + \lambda \sin \phi)\,R$$

where $\lambda = 0$ the sphere $\lambda = 1$ paraboloid $\lambda > -1$ ellipsoid Equation (A2) is therefore written as

$$\frac{u}{kR} = \frac{1}{E}(\sigma \quad - \mu(\ _{\phi\phi} + \quad)) \quad (A5)$$

Equating (A5) and (A3) gives

$$\sigma_{\phi\phi} = \left(\frac{k + \mu}{1 + k\mu}\right)\sigma_{\theta\theta} + \mu\frac{(1 - k)}{(1 + k\mu)}\sigma \qquad (A6)$$

For simplicity

$$\sigma_{\phi\phi} = C\ (\mu\ \phi)\ \sigma_{\theta\theta} + C\ (\mu, \phi)\ \sigma \qquad (A\ )$$

By differentiating (A3) with respect to R and equating the result to (A1) the following equation is obtained

$$R\frac{d}{dR}(\sigma_{\phi\phi} - \mu(\sigma \quad + \sigma_{\theta\theta}))$$

$$= (1 + \mu)(\sigma \quad - \sigma_{\phi\phi}) \qquad (A8)$$

If (A7) is substituted into (A8) then

$$R\frac{d}{dR}((C \quad - \mu)\sigma \quad + (C \quad - \mu)\sigma \quad)$$

$$= (1 + \mu)(\ (1 - C\ )\sigma \quad - C\ \sigma_{\theta\theta}) \quad (A9)$$

r in (A4) is replaced by kR and the whole equation is divided by kR,

$$\frac{1}{R}\frac{d}{dR}(\sigma \quad R^2) - \frac{\sigma_{\theta\theta}}{k} - \sigma_{\phi\phi} = 0 \qquad (A10)$$

Equation (A7) is substituted into (A10) after $\sigma_{\phi\phi}$ is expressed in terms of σ_R and $\sigma_{\theta\theta}$.

$$\sigma \quad = \frac{1}{\left(C \quad + \frac{1}{k}\right)}\left(\frac{1}{R}\frac{d}{dR}(\sigma \quad R^2) - C_i\sigma \quad\right) \qquad (A11)$$

After $\sigma_{\theta\theta}$ in Equation (A9) is replaced by Equation (A11) a differential equation of σ_{RR} as a function of R for a particular ϕ is obtained

$$R\frac{d}{dR}\left(\frac{C \quad - \mu}{C \quad + \frac{1}{k}}\left(\frac{1}{R}\frac{d}{dR}(\sigma_{RR}R^2) - C\ \sigma \quad\right) + (C \quad - \mu)\,\sigma_{\ R}\right)$$

$$= (1 + \mu)\left((1 - C\ )\sigma \quad - \frac{C}{C_1 + \frac{1}{k}}\left(\frac{1}{R}\frac{d}{dR}(\quad R\ ) - C\ \sigma \quad\right)\right)$$

$$R\frac{d}{dR}\left(\left(\left(\frac{C \quad - \mu}{C \quad + \frac{1}{k}}\right)\frac{1}{R}\frac{d}{dR}(\quad R^2)\right) + \left((C \quad - \mu) - \frac{(C \quad - \mu)}{C \quad + \frac{1}{k}}\right)\sigma \quad\right)$$

$$= (1 + \mu)\left(\left((1 - C\ ) + \left(\frac{C\,C}{C \quad + \frac{1}{k}}\right)\right)\sigma \quad - \left(\frac{C}{C \quad + \frac{1}{k}}\right)\frac{1}{R}\frac{d}{dR}(\sigma_R \quad R^2)\right)$$

$$R \frac{d}{dR}\left(\frac{\alpha}{R}\frac{d}{dR}(\sigma_{RR}R^2) + \beta\sigma_{RR}\right) = \gamma\sigma_{RR} - \frac{\delta}{R}\frac{d}{dR}(\sigma_{RR}R^2) \qquad (A12)$$

where $\alpha = k(1-\mu)$, $\beta = k\mu(1+k)$, $\gamma = (1-\mu+3k\mu+k^2)$, $\delta = k(k+\mu)$. A transformation of $X = R^2\sigma_{RR}$ is introduced into Equation (A12) which after simplification becomes

$$R\frac{d}{dR}\left(\frac{\alpha}{R}\frac{dX}{dR} + \frac{\beta X}{R^2}\right) = \frac{\gamma X}{R^2} - \frac{\delta}{R}\frac{dX}{dR}$$

$$\alpha X'' + (-\alpha + \beta X + \delta)\frac{X'}{R} - (2\beta + \gamma)\frac{X}{R^2} = 0 \qquad (A13)$$

where X' denotes $\frac{d}{dR}$ and X'' $\frac{d^2}{dR^2}$. Since $(-\alpha + \beta + \delta) = 0$, Equation (A13) is reduced to

$$X'' - \left(\frac{2\beta + \gamma}{\alpha}\right)\frac{X}{R^2} = 0 \qquad (A14)$$

Putting $\frac{2\beta+\gamma}{\alpha} = \frac{n^2-1}{4}$, Equation (A14) is satisfied by

$$X = AR^{\text{[illegible]}} - BR^{\text{[illegible]}}$$

where A and B are arbitrary constants. Therefore, the radial stress is

$$\sigma_{RR} = AR^{\text{[illegible]}} - BR^{\text{[illegible]}} \qquad (A15)$$

For a certain angle ϕ = constant, the endocardial radius of curvature is R_o, the thickness T, and the internal pressure $-P$. The boundary conditions are

$$\sigma_{RR} = -P \text{ at } R = R_o$$

$$= 0 \text{ at } R = R_o + T$$

$$-P = AR_o^{\text{[illegible]}} - BR_o^{\text{[illegible]}}$$

$$0 = A(R_o + T)^{\text{[illegible]}} - B(R_o + T)^{\text{[illegible]}}$$

Hence

$$A = \frac{PR_o^{\text{[illegible]}}}{(R_o + T)^{n} - R_o^{n}}$$

$$B = \frac{PR_o^{\text{[illegible]}}(R_o + T)^{\text{[illegible]}}}{(R_o + T)^{n} - R_o^{n}}$$

When these constants are substituted in Equation (A15) the radial stress is found to be

$$\sigma = \frac{PR_e}{(R_e + T) - R_e} R \left(1 - \frac{(R_e + T)}{R}\right) \qquad \text{(A16)}$$

The latitudinal stress can be found from Equation (A10). After differentiating σ_{RR} with respect to R and simplifying, the latitudinal stress takes the following form

$$\sigma = \frac{1}{C + \frac{1}{k}} \frac{PR_e}{(R_e + T) - R_e} R \left(\left(\frac{n+1}{2} - C\right) + \left(C - \frac{1-n}{2}\right)\left(\frac{R_e + T}{R}\right)\right)$$

(A17)

The longitudinal stress $\sigma_{\phi\phi}$ is given by Equation (A6) which is

$$\sigma_{\phi\phi} = C\,\sigma\,\sigma + C\,\sigma$$

$$= \frac{PR_e}{(R_e + T) - R} R \left(\frac{C}{C + \frac{1}{k}}\left(\frac{n+1}{2} - C\right) + C + \left(\frac{C}{C + \frac{1}{k}}\left(C - \frac{1-n}{2}\right) - C\right)\left(\frac{R_e + T}{R}\right)\right) \qquad \text{(A18)}$$

Laplace's Law. The formulas for the latitudinal and the longitudinal stresses given in Equations (A17 and A18) show that the magnitudes of the stresses vary from layer to layer within the heart wall. However, if the thickness of the wall is small in comparison with the radius of curvature, Equations (A17 and A18) will reduce to a form analogous to the ordinary Laplace's Law.

For a very thin wall, the ratio of the thickness to the radius of curvature is much smaller than unity, and the radius of curvature (R) is roughly equal to the sum of the endocardial radius of curvature (R_e) and the thickness of the wall (T). Mathematically, when

$$\frac{T}{R} << 1$$

then

$$R \simeq R_e + T \text{ and } R \simeq R_e$$

Expanding Equations (A17) and (A18) by Taylor's expansion and neglecting expressions for the nonlinear terms, i.e.

$$\left(1 + \frac{T}{R}\right) \simeq 1 + n\frac{T}{R}$$

$\sigma_{\phi\phi}$ and σ are reduced respectively to

$$\sigma = \frac{1}{\left(C + \frac{1}{k}\right)} \frac{PR}{T}$$

$$\sigma_{\phi\phi} = \frac{C}{C + \frac{1}{k}} \frac{PR}{T}$$

and

$$\frac{\sigma}{r} + \frac{\sigma_{\phi\phi}}{R} = \frac{P}{T}\left(\left(\frac{R}{r} + C\right)\frac{1}{C + \frac{1}{k}}\right) \qquad \text{(A19)}$$

Since the two radii of curvature are related by r = kR or $\frac{r}{R}$ = k, the term within

the bracket becomes unity Equation (A19) is equal to

$$\frac{t_{\theta}}{r} + \frac{t_{\phi\phi}}{R} = P \qquad (A20)$$

$$t_{\theta\theta} = \sigma_{\theta\theta} \quad T$$

$$t_{\phi\phi} = \sigma_{\phi\phi} \quad T$$

where $t_{\theta\theta}$ and $t_{\phi\phi}$ are longitudinal and latitudinal tensions, respectively Equation (A20) is equivalent to the Law of Laplace for a membrane under tension

The authors are grateful to Dr. C. Miller, Nova Scotia Technical College, for helpful suggestions and criticism

REFERENCES

1 Laplace, P. S. Theorie de l'action capillaire. *In* Traité de Mecanique Céleste Supplement au livre X, Paris, 1805 Courcien
2 Wood, R. H. A few applications of a physical theorem to membranes in the human body in a state of tension J. Anat Physiol. 26:302 1892
3 Burton, A. C. The importance of the shape and size of the heart Am. Heart J 54:801 1957
4 Rushmer, R. F., and Thal, N. The mechanics of ventricular contraction, Circulation 4:219 1951
Wilson, M. F. Analysis of ventricular dimension in the unanesthetized dog Circulation Res. 16:249 1965
6. Hawthorne, E. W. Dynamic geometry of the left ventricle Am. J. Cardiol. 18:566, 1966
7 Sandler, H., and Dodge, H. T. Left ventricular tension and stress in man, Circulation Res. 13:91 1963
8. Kreuzer, H., and Schoeppe, W. Die Drucküberträgung in der Wand des toten Herzens Pflügers Arch. ges. Physiol. 278:221 1963
9 Kreuzer, H., and Schoeppe, W. Das Verhalten des Druckes in der Herzwand Pflügers Arch ges. Physiol 278:181 1963
10. Spotnitz, H. M., Sonnenblick, E. H., and Spiro, D. Relation of ultrastructure to function in the intact heart. Sarcomere structure relative to pressure volume curves of intact left ventricles of dog and cat, Circulation Res. 18:49 1966
11 Linzbach, A. J. Heart failure from point of view of quantitative anatomy Am. J. Cardiol. 5:370 1960.
12 Badeer, H. S. Biological significance of cardiac hypertrophy Am. Heart J. 60:918, 1960.
13 Gould, S. E. Pathology of the heart, ed. 2, Springfield, Ill, 1960 Charles C Thomas, Publisher pp 333-539
14 Kerr, A. J., Winterberger, A. R., and Giambattista, M. Tension developed by papillary muscles from hypertrophied rat heart, Circulation Res. 9:103 1961
15 Beznak, M. Cardiac output in rat during the development of cardiac hypertrophy Circulation Res. 6:207 1958.
16. Grimm, A. F., Kubata, R., and Whitehorn, W. V. Properties of myocardium in cardiomegaly Circulation Res. 12 118, 1963
17 Sonnenblick, E. H. Implications of muscle mechanics in the heart Fed Proc 21:975 1962.

Case reports

Isolated massive chylopericardium

Stephen P Glasser Captain MC USA
Melvin D Cheitlin Lieutenant Colonel MC USA
*Lee S Serfas Colonel MC USA ***
*Sheldon S Sbar Captain MC USA ***
Honolulu H wa

There have been only 10 cases of isolated massive chylopericard um e ported m the world s l terature Three of these[1] were secondary to mediastinal lymphangiomatous hamartomas Only 5 cases were truly idiopathic ance in the remaining cases lymphangiectasis was observed apparently connecting the pericar dium to the thoracic duct The first case of chylopericardium was described by Hase brock in 1888 in a patient with tracheal stricture and ulceration who at postmor tem examination had 0 .c of chyle in the pericardial sac The first case of massive chylopericardium was described by Groves and Effler[4] in 1954 That this ent ty might not be as are as was formerl thought is suggested by a ase of Holman and Stein berg In a patient presented to demonstrate the role of angiocardiogr ph n the surgical treatment of massive pericardial effusion 1,000 c of m lky fluid was aspir ted at operation f om an 11 ear-old Egyptian boy The stated that a variety of studies of th peri ardium and fluid failed to establish th use of the effusion "

It is the purpose of this paper to review these ten cases and present the eleventh case of isolated massive chylopericardium.

Case report

A 23-year-old Negro woma as first seen on June 7 1966. She had reported her dispensary in early April, 1966 for general ph sical examination and at that time outine chest -ray as taken. Because of an enlarged cardiac silhouette, she referred to the Cardiology Clinic for further ev lua tion. On initial questioning, she was entirel as mptomatic, specificall denying shortness of breath dyspnea on exertion orthopnea ankle edema chest pain, cough, paroxysmal nocturnal d spnea, or nocturia She also denied onstitutional s mptoms skin rashes, arthritis arthralgias tuberculou ex posure, or chest trauma I retrospec and only after he as are of the -ray abnormality she did admit some eas f tigability during m of her lif but increasi g over the preced ng several months. A routine berculosis survey hes -r two years prior as eported to her norm l I M 1966 she had been trea ed for mon cal vaginitis with \ a lh and tetrac line

The physical examina on revealed healthy appearing Negro oman in no distress Her blood pressure was 1?0 0 mm Hg thou pulsu para doxus Her pulse 63 per m nu and regular and her temperature 98.6 F The neck eins

Received or pu ca May 967
This paper was read bef re the American College of Cardiology meeting in Honolulu Hawaii, Feb 5 196
*Chief Reside Internal Medicine Tripler General Hospital Honolulu, Hawaii
**Chief ology Service T ipler General Hospital, Honolulu Hawaii
***Chief eneral Surgery and Thoracic Surgery Services Tripler General Hospital Honolulu, Hawaii
****Assis ac hief ardiology Service, Tripler General Hospital, Honolulu Hawaii

the bracket becomes unity Equation (A19) is equal to

$$\frac{t_{\theta}}{r} + \frac{t_{\phi\phi}}{R} = P \qquad \text{(A20)}$$

$$t_{\theta} = \sigma_{\theta\theta} \quad T$$

$$t_{\phi\phi} = \sigma_{\phi\phi} \quad T$$

where t_{θ} and $t_{\phi\phi}$ are longitudinal and l titudi al tensions, respectively Equation (A20) is equi alent to the Law of Laplace for membr ne under tension

The authors re grat f l to Dr C Miller Nova S otia Tech ic l College for helpful suggestions nd criticism

REFERENCES

1 Laplace P S Théorie de l'action capillaire I T aite de Mecanique Céleste Supplement livre X Paris, 1805 Courcier
2 Wood, R H A few pplications of physical heorem t membr nes i the h man body in tat of tension J Anat Physiol 26:302, 1892
3 Burton A C The mportance of the shape nd size of the heart Am Hr rt J 54:801 1957
4 Rushmer R F nd Thal, N The mechanics of ve tricula contraction, Circulation 4:219 1951
5 Vnon a, I nd Wilson M F Analyses of entricular dimension n the unanesthetized dog Circulation Res 16:249 1965
6. Hawthorne E. W Dynamic geometry of the left ventricle Am. J Cardiol. 18:566, 1966
7 Sandler H and Dodge H T Left ventricular tension and stress in ma Circulation Res. 13:91 1963
8. Kreuzer H and Schoeppe W Die Druckü bertragung in der Wand des toten Herzens, Pflugers Arch ges. Physiol. 278:221 1963.
9 Kreuzer H and Schoeppe W : Da Verhalten des Druckes i der herzwand, Pflugers Arch. ges. Physiol. 278 181 1963
10. Spotnitz, H M Sonnenblick, F H and Spiro, D Relation of ultrastructure t function in the intact heart Sarcomere structure relative t pressure volume curves of intact left ventricles of dog and cat, Circulation Res 18:49 1966
11 Linzbach A. J Heart failure from point of view of quantitative anatomy Am J Cardiol 5:370 1960
12 Badeer H S. Biological significance of cardiac hypertrophy Am HEA T J 60:918, 1960.
13. Gould, S E Pathology of the heart ed. 2, Springfield, Ill 1960, Charles C Thomas, Publisher pp. 533-539
14 Kerr A J Winterberger A. R and Giambattista, M Tension developed by papillary muscles from hypertrophied rat heart Circulation Res 9 103 1961
15 Beznak M Cardiac output in rats during the development of cardiac hypertrophy Circulation Res. 6:207 1958.
16. Grimm A F Kubota R., and Whitehorn, W V Properties of myocard m in cardiomegaly Circulation Res. 12 118, 1963
17 Sonnenblick, E. H. Implications of muscle mechanics in the heart Fed Proc 21:975 1962.

Table I. Catheterization data

Location	Mean	Pressure (mm. Hg)		O₂ saturation (per cent)
		Systolic	Diastolic	
Superior vena cava				73
Right atrium	6			74
Right ventricle		26	2 7	76
Pulmonary artery	14	26	10	76
Pulmonary artery wedge	9			96

After pericardiocentesis, the mean ... pressure was 2 ... mm. H



Fig. 3. Angiocardiograph showing massive pericardial effusion.



Fig. 4. Chest roentgenogram following injection of 300 c.c. of air after pericardiocentesis shows normal-sized heart and otherwise normal-appearing pericardial lining (Arrow).

tenseness. The heart did not appear float in the fluid. Examination of the superior posterior aspect of the hilum of the left lung revealed approximately fiv dilated chyle-containing lymphatic vessels each approximately 5 cm. long and between 3 and 5 mm. in diameter. They were located over the superior and posterior aspects of the left pulmonary artery extrapericardially and subpleurally. Close examination of the remainder of the pleural ... revealed no abnormalities. No tumors were palpable and no ... channels appeared ... abnormal. Eight ounces of ... drink composed of half milk and half cream, with 3 c.c. of 4 per ... sky-blue ... mixture had been given ... the patient ... hours before she was brought to the operating room. No evidence of dye was seen during the operation even in the thoracic duct ... the diaphragm. Then 800 ... of chyle ... aspirated from the pericardial sac.

this fluid had the typical appearance of milk (Fig. 6). The inner surface of the pericardium was ... and smooth. The thoracic duct was then exposed and appeared normal in diameter. Saline was injected ... both directions, and no evidence of leakage could be found. Then 2 ... of sky-blue ... injected in the duct. Within 5 minutes, the dilated tortuous lymphatic channels on the superior and posterior aspect of the left hilum filled with dye (Fig. ...). Within 10 minutes the entire intrapericardial portion of the main pulmonary artery became evenly stained with dye. There was no evidence of dye dripping into the pericardial sac and no demonstrable dilated lymphatics. ... appeared as though transudation had occurred. Just lateral to the fold of Marshall, an intrapericardial cul-de-sac was formed, in the depths of which ... 1 mm. sinus opening. A drop of dye came from this opening on ... occasions. There was staining of the pericardium simultaneously with and of equal intensity to that seen on the pulmonary

Table II

Appearance	Milky
Specific gravity	1.045
White blood cell count	4,000 per cu mm (all lymphocytes)
Red blood cell count	4,300 per cu mm
Protein	7.2 Gm per cent
Glucose	105 mg per cent
Cholesterol	172 mg per cent
Transaminase	100 units
Chloride	107 mg per liter
Lupus erythematosus preparation	Negative
Gram stain	No organisms
Acid-fast bacillus	No organisms
Aerobic culture	No growth
Anaerobic culture	No growth
Acid-fast bacillus culture	No growth
Microscopic examination	No crystals. Tiny fat droplets stained with Sudan III were present in Brownian motion



Fig. 5. Chest roentgenogram showing reaccumulation of fluid six days after pericardiocentesis.

artery. A polyethylene catheter was inserted for a distance of 1 cm. Its end was then ... the area of the dilated lymphatics over the extrapericardial left pulmonary artery but not within the lumen of dilated lymphatic. There were no abnormal lymphatic vessels or dye staining over the esophagus or elsewhere in the mediastinum. The tortuous lymphatic channels in the hilum were ligated and the thoracic duct was doubly ligated just above the diaphragm. A 5 by 10 cm. pericardial window was formed and the chest was closed. The patient had an uncomplicated postoperative course and a chest x-ray six days later revealed a normal-sized heart. Within two weeks, the cardiac silhouette increased to almost twice normal size but it began shrinking spontaneously before further studies were performed and was normal seven months postoperatively (Fig. 6). It is, therefore, uncertain as to whether this represented a reaccumulation of chyle or serous fluid accumulation. The important point to emphasize from a surgical aspect is that, although a large pericardial window was formed, the redundancy of the pericardium apparently allowed the edges to reapproximate. This should have been avoided by making a larger pericardial window or by pericardiectomy. Gross and histological examination of the thoracic duct and pericardium revealed no abnormalities.

Discussion

In 1935 Yater[1] in his article on chylothorax concluded that traumatic chylothorax was less common than the nontraumatic forms. This has since been disputed, however, and trauma and tumor lead the list as the causes of chylothorax either alone or in combination with chylopericardium. The other causes that have been mentioned are superior vena cava obstruction, posterior mediastinal lymphomas, tuberculosis, lymphangiectasis, polyserositis, and cirrhosis.

The lymphatic vessels draining the epicardial, myocardial, and subepicardial plexuses of the heart are a loosely arranged network in the subepicardial connective tissue. These small lymphatic channels drain into several rather constant lymphatic channels of larger size. All the lymphatic channels draining the subepicardium and the myocardial and subendocardial plexus then unite in a single common lymphatic trunk and drain into the left mediastinal plexus of vessels.[19] No large connections between the pericardium and the thoracic duct have been demonstrated, but it seems obvious that these connections do exist. Dilated lymphatics on the posterior pericardial surface apparently draining toward the thoracic duct have been described at operation in cases of esophageal carcinoma, and in one of the reported cases of isolated chylopericardium[3] dilated lymphatics were seen coursing from the pericardial surface towards the thoracic duct. However, it is believed that these drain into the mediastinal lymph nodes, and then in turn drain into the thoracic duct. The pericardial lymphatic plexus

Fig. 6





Fig. 7



F



Fig. 8. Posteroanterior chest roentgenogram seven months after operation is normal except for changes in the left costophrenic angle which are secondary to the operation.

drains the lymphatic channels in the anterior mediastinum to the right lymphatic duct and the thoracic duct on the left.[11]

Since the pericardial lymphatics drain into the thoracic duct there is an apparent connection and it would seem that obstruction of the thoracic duct would be the common denominator of most of the cases of chylothorax and chylopericardium. It soon becomes apparent that it is not as simple as this for several reasons. (1) Many cases of thoracic duct obstruction are unassociated with the accumulation of chyle. (2) Stuart found many variations of the communications between tributaries of the thoracic duct and the venous system with ample collaterals directly into the venous system, especially with cross connections to the channels draining into the right lymphatic duct. (3) Stuart also found that in some instances the thoracic duct was not a single channel. (4) Finally, it is well known that the thoracic duct can be ligated cephalad to the heart and mediastinum without causing chylothorax or chylopericardium.

Considerable discussion has been generated as to the mechanism of chylous effusion. Bartel and Nettler[4] suggest the possibility of increased permeability of the lymphatic vessel wall of unknown etiology, a loss of smooth muscle tonus possibly on a reflex basis or a congenital defect. Since there was no enlargement of the thoracic duct or other abnormal lymphatics, as might be expected with proximal duct obstruction, transudation through lymphatics of increased permeability would seem to be the most logical way in which chyle entered the pericardial sac in our patient. In the last analysis, except possibly for the cases of cystic hygromas, no satisfactory explanation is present, although a congenitally abnormal connection (or potential connection) would seem also to be a possibility. Neither in his nor our patient was a demonstrable gross or histological change observed in the thoracic duct.

Chylous fluid is characterized by two main features. Its milky white appearance can be confused with almost nothing else (Fig. 9) and microscopically one sees fat droplets (especially with fat stains) in Brownian movement. It is alkaline, usually has a specific gravity of 1.018 to 1.025 (although in our patient it was 1.045) and usually contains white blood cells, primarily lymphocytes. It contains a significant amount of protein and lipids but this and the other constituents are determined primarily by the diet. It is bactericidal so one can assume that infections of chylous effusions will rarely occur and chance of infection from aspiration or surgical procedures is unlikely.

Once a pericardiocentesis is performed and the typical fluid obtained, there is usually little to consider in differential diagnosis. Cholesterol pericarditis is the major consideration. In this, the fluid has a golden hue and its hallmark is the presence of cholesterol crystals. Cholesterol pericarditis has been associated with hypertension, tuberculosis, carcinoma, mitral stenosis, arthritis, and atrial septal defect.[12]

Review of the eleven cases

See Tables III, IV, and V for summary of the data. The sex incidence is about equal. The predominating symptom was dyspnea, which was present in some form in six of the cases although at least four patients were asymptomatic. Evidence of cardiac tamponade was present initially in three; the precordial activity was diminished in five, not mentioned in three, and normal in only one. In our case on

Table III

Case	Age	Sex	Race	Symptoms	Signs	Laboratory ECG	White blood cells/cu.
Groves and Effler[1]	31	F	—	Dyspnea, choking, dizziness	Active precordium, engorged neck veins	Low voltage	3,850
[illegible][2]	1	F	—	Dyspnea	Tachycardia	Pericarditis	6 900
Madison and Logue[3]	40	F	—	Mild dyspnea	Apical impulse absent, heart sounds normal, venous pressure 110	Low voltage	10,200
Stratton and Grant[4]	Infant	F	—	Respiratory distress	—	—	—
Miller and associates[5]	15	F	W	Orthopnea, dyspnea	Apical impulse absent, heart sounds distant, venous pressure 365, pulsus paradoxus present	Low voltage	3 650
Hurt and Nettles[6]	6	M		Asymptomatic	Heart sounds distant	Decreased voltage compared to postoperative	—
Knight[7]	60	M	W	Dyspnea, cough fatigability	Heart sounds faint, moderate jugular venous distension	Low voltage, flat T I, and VL	4 300
Holdsworth and Miller[8]	22	M	W	Asymptomatic	Heart sounds normal, decreased apical impulse	Normal limits	Normal limits
Yiakoupoulos and coworkers[9]	40	M	W	Asymptomatic	Cardiac impulse absent, apical protodiastolic gallop	Normal limits	8 500
F[illegible]al and coworkers[10]	38	M	W	Epigastric and substernal fullness and discomfort	Apical pulse not palpable heart sounds distant	Normal limits	9 800
Present case	23	F	N	Questionable easy fatigability	Normal physical examination	Normal limits	3,200 to 6,800

Table IV. Pericardial fluid

Reference No.	Specific gravity	Protein (Gm. per cent)	RBC	WBC per cu. mm.	Culture	Cholesterol (mg. per cent)
1	1 018	3 15	800	600 (1 lymphocyte)	Neg	131
2		4 2	—	—	—	118
3	1 014	5 4	—	2 750 lymphocytes	Neg	140
4	—	—	—	—	—	—
5	1 0_5	4 9	—	—	Neg	103
6	—	—	Few	Few lymphocytes	Neg	
7	—	—	—	—	Neg	—
8		"Typical for chyle"				
9	—	8 8	10 300	4 400 90 per cent lymphocytes	Neg	125 160
10	1 036	5 9	8 000	280 lymphocytes	Neg	103
Present case	1 015	—	4 300	4,000 [illegible] lymphocytes	Neg	172

Table V

Reference No.	*Etiology*	*Treatment*	*Result*
1	Lymphangiomatous hamartoma (hygroma)	Ligation of thoracic duct and pericardial window, removal of hygroma	No reaccumulation at 6 mo. after second operation
2	No connection, no abnormalities	Ligation of thoracic duct and surrounding tissue including azygos vein	No reaccumulation
3	Large lymphatic channel	Ligation of thoracic duct, dilated channels, and pericardial window	No reaccumulation
4	Lymphangiomatous hygroma	Dissection of mass and pericardial window	Reaccumulation and death
5	Multiple large branching lymphatics (lymphangiomatous hamartoma with lymphangiectasia of lungs, pleura, and pericardium)	Pericardial window and ligation of dilated lymphatics	Reaccumulation and death
6	Normal thoracic duct, numerous collaterals demonstrated by methylene blue injection	Ligation of thoracic duct with pericardial window	No reaccumulation at 3 mo.
7	None	Ligation of thoracic duct with pericardial window	No reaccumulation
8	None	Pericardiectomy and ligation of thoracic duct	No reaccumulation at 14 mo.
9	None	Pericardiectomy and ligation of thoracic duct	No reaccumulation at 17 mo.
10	None—thoracic duct identified	Ligation of lymphatic channels. Hemipericardiectomy	No reaccumulation 6 mo.
Present case	Lymphangiectasia	Ligation of thoracic duct collaterals, and pericardial window	No reaccumulation at 7 mo.

At initial operation a 4 cm. pericardial window was made but within 3 mo. reaccumulation occurred

physical examination the precordial activity was normal and the heart sounds distinct which initially led us away from the diagnosis of pericardial effusion. There was no evidence of right-sided failure. The specific gravity of the chyle (1.045) would be the most likely explanation for this, in that it is theorized that the high specific gravity of the fluid allowed the heart to float towards the chest wall. This was not observed at the time of the operation; however, a specific gravity of the fluid aspirated at surgery was not obtained and was probably lower since the patient had been without food for 12 hours prior to surgery. A cadaver heart containing blood was placed in a solution with a specific gravity of 1.045 and was noted to float. Although at cardiac catheterization the pressures in the right ventricle and atrium were normal, they were lower after pericardiocentesis. It is also interesting that three of the reported cases had a mild leukopenia and in our patient the admission white count was 3,200 per cubic millimeter, although by the next day it was again normal. Results of the remaining laboratory tests were normal except in two cases in which the intermediate PPD skin test was positive. In six cases the ECG had low voltage (in one case it was not done) and in three it was normal (in our case again possibly explained best on the basis of the heart floating towards the chest wall). The voltage was greater after surgery in our patient. The appearance of the pericardial fluid was typical of chyle and was free of cholesterol crystals in all cases.

Lymphangiomatous hamartomas (cystic hygromas) of the mediastinum are rare in and of themselves, with only 20 reported cases. They were present in 3 cases,[1]

and dilated lymphatic channels coursing from the pericardium toward the thoracic duct were present in 2 cases [9] other than our own The etiology in 6 of the 11 cases, therefore was explained whereas in 5 of the cases there were no demonstrable abnormalities In the case of Fawal and associates no thoracic duct was demonstrable Only two of the patients reported died [5] in both of these there were hamartomas and both had surgical procedures which did not include thoracic duct ligation One of the reported cases was treated initially with a 4 cm pericardial window through a left thoracotomy The chyle was not recognized and the patient was treated with antituberculous drugs. Within three months there was complete reaccumulation of chyle and the return of symptoms Reoperation through the right side of the chest revealed a cystic hygroma of the mediastinum with a chylopericardium Treatment consisted of construction of a larger pericardial window partial excision of the cystic hygroma and ligation of the thoracic duct at the level of D 10 There was no further reaccumulation. All of the cases successfully treated have had ligation of the thoracic duct above the diaphragm performed as a part of the treatment and it is felt that this is absolutely necessary to guard against recurrence

Finally of the two usually feared complications of pericardial effusion—acute tamponade and constrictive pericarditis—only the former occurred with any regularity (three of nine in which this was mentioned) and constrictive pericarditis was not reported in any of the cases, although the longest follow up was only 4 years.

Summary

The eleventh case of isolated massive chylopericardium is presented and the ten other cases reported in the world's literature are discussed About half of the cases are secondary to either mediastinal lymph angiomatous hamartomas or mediastinal lymphangiectasis, but in the remaining cases no cause could be found

In most cases, with proper diagnosis and therapy the prognosis is excellent but therapy must include a large pericardial window or even hemipericardiectomy and ligation of the thoracic duct just above the diaphragm

REFERENCES

1. Groves, L. K., and Effler D B. Primary chylopericardium, New England J Med 250:520, 1954
2. Naef A. P Primary chylopericardium and its surgical treatment, Dis. Chest. 30 160, 1956.
3. Madison W M and Louge, B Isolated ("primary") chylopericardium, Am. J Med 22:825 195
4. Stratton V C. and Grant R. N: Cervicomediastinal hygroma associated with chylopericardium, Arch Surg 77:887 1958.
5. Miller S. V Pruett, H J and Long, A. F tal chylopericardium caused by hamartomatous lymphangiomatosis, Am. J Med. 26:951 1959
6. Bartel, V J and Nettler E. Das Isolierte Chyloperikard Cardiologia (Basel) 45:251 1964
7. Knight, H F Primary chylopericardium J Thoracic & Cardiovas. Surg 80:567 1956
8. Hudspeth, A. S., and Miller H S.: Isolated (primary) chylopericardium J Thoracic & Cardiovas Surg 51:528 1966.
9. Yiokopoulos, N A., Akbarian, N Starkby W B and Abelman W H Isolated chylopericardium diagnosis, hemodynamic studies and surgical treatment Am. J Cardiol. 19 440, 1967
10. Fawal I A. Kirkland, L. Dykes, R., and Foster G. L. Chronic primary chylopericardium report of a case and review of the literature Circulation 35 777 1967
11. Yater W M: Nontraumatic chylothorax and chylopericardium Ann. Int. Med. 9:600, 1936.
12. Lahoda, A. A. Development and structure of the cardiovascular system, New York, 1961 McGraw Hill Book Company Inc., pp. 110-111
13. Brawley R K., Vasko, J S., and Morrow A. G. Cholesterol pericarditis, Am J Med 41:235 1966.
14. Holman C. W and Steinberg, I The role of angiocardiography in the surgical treatment of pericardial effusions, Surg., Gynec., & Obst. 107:639 1958

The Wolff Parkinson White syndrome

Report of a case with fatal arrhythmia and autopsy findings of myocarditis, interatrial lipomatous hypertrophy and prominent right moderator band

Benjamin B Okel M.D
Decatur Ga.

The Wolff Parkinson-White (WPW) syndrome is usually regarded as a benign curiosity significant only in that a variety of arrhythmias are likely to occur and that misdiagnosis of myocardial infarction is an easy pitfall. However the medical literature records several sudden and unexpected deaths in these patients. The case which is herein reported again illustrates the lethal potentiality of this anomaly. In addition, this case at autopsy revealed hypertrophy of a portion of the right ventricular musculature and suggests the interesting possibility of anomalous AV conduction being a cause of idiopathic ventricular hypertrophy.

Case report

A 33-year-old Caucasian man arrived at the DeKalb General Hospital emergency room complaining of sudden onset of rapid heart action approximately one hour previously. Six years previously he experienced a similar episode lasting approximately 18 hours and requiring hospitalization at another institution. Telephone communication with the ECG department of this hospital revealed that the patient had then been in atrial fibrillation with rapid ventricular response. After digitalization and on conversion to normal sinus rhythm he was noted to have WPW conduction (Fig 1). The patient related that he had continued taking digitalis for approximately three years thereafter and had experienced no disturbances of heart rhythm until the present admission. He denied recent illness, though his wife volunteered that he had recently worked long hours as a machinist and had seemed physically exhausted for several days.

Examination revealed a well-developed but pale Caucasian man in mild respiratory distress. He complained of tightness in his chest, but denied true pain. The brachial blood pressure was 100/60 mm. Hg and the radial pulse approximately 100 per minute. The neck veins were not distended and the lung fields were clear. Cardiac auscultation revealed a rapid irregular rhythm at approximately 170 per minute. No definite murmurs were heard, but low-pitched muffled extra sounds were inconsistently present.

The electrocardiogram (ECG) (Figs 2 and 3 A) showed wide ventricular complexes at 200 to 220 per minute. Initial treatment consisted of sedation and 0.5 mg of digoxin intravenously. The latter was repeated after two hours. The patient showed symptomatic improvement and the apical pulse apparently slowed to approximately 100 per minute. However his ECG (Fig 3,B and C) showed an increase in the number of ventricular complexes per minute. Preparations were being made for elective electrical conversion when the patient suddenly convulsed and ceased breathing. An ECG rhythm strip revealed ventricular fibrillation (Fig 3,D). Direct current defibrillation was successful, but the resulting slow sinus pacemaker (Fig 3,E) yielded no effective heartbeat and resuscitation attempts were unsuccessful.

At autopsy the lungs showed acute passive congestion and edema. The significant necropsy

From the ECG Department of DeKalb General Hospital, Decatur Ga., and the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

Received for publication May 29 [illegible]

*Instructor in the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

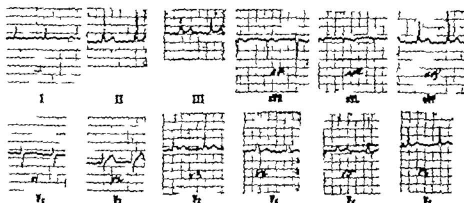


Fig. 1. ECG of Dec. 24, 1960 showing W-P-W conduction.

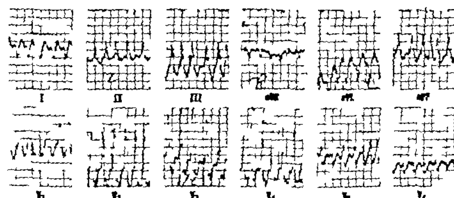


Fig. 2. ECG of Nov. 26, 1966 showing trial fibrillation, anomalous AV conduction ad rapid entricular re ponse.

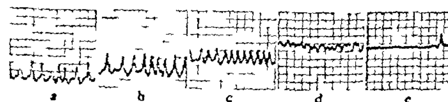


Fig. 3. Lead II ECG rips on Nov. 26, 1966 (A) t 8:30 A.M. (B) t 10:30 A.M. (after 0.50 mg. of digoxin i tra enously), (C t 4:00 P.M. (after 1.0 mg. of digoxi intra enously) (D) at 6:20 P.M. and t (E) 6:22 P.M. (af er electric l defibrillation).

find ngs were otherwise limited t the heart F tern l examina ion ppe red essentially normal. The heart weighed 590 gram The coronary arteries were patent nd almo t free of herosclerosis. There w an incre se th kness i the interatrial sept m in the are bos the oronary sinu and p terior t the foramen ov le Gross section re- led this to be i ter trial septal "Lipoma" mea uring pproximately cm i diameter Further examination of the ri ht side of the heart rev led

l rge muscle band (Fig. 4) di id g the right en- tricle i t t c ties This mod fied moderator band ppe red t markedly obstruct the outflow t act of the right entricle It was not the usual moder tor band i that t w l continuation with the t beculae of the muscle wall nd separ ted the true entricul ity from the outflow tract.

The entire heart w preserved nd examined further by Dr William C M on the Armed Forces Instit t of P thology A study of the on-



Fig. 4. View of right ventricular cavity demonstrating the obstructing muscle band.



Fig. 5. Section of atrial septum showing myocarditis.

duction system was made using blocks from the atrial septum as suggested by Widran and Lev. In addition, eight blocks were taken from the region of the junction of the superior vena cava and the right atrium and a block was taken from the "lipoma" of the interatrial septum. The AV node was identified, as was the common bundle, and the right and left branches. Sections from the atrial "lipoma" revealed a marked increase in adipose tissue in the interatrial septum with evident loss of muscle and fatty replacement. Since there was no capsule or limiting membrane, this was not considered a true lipoma. Fatty infiltration of the bundle of His was evident. No accessory atrioventricular muscle connections could be identified. The most surprising histologic finding was a diffuse inflammatory process involving both atrial and ventricular portions of the septum, though heavier in the atrial portion (Fig. 5). The inflammatory infiltrate of mononuclear leukocytes appeared in some areas to be in relationship to the bundle, but for the most part, the node and common bundle appeared uninvolved.

Discussion

It is assumed that the myocarditis in this case precipitated the atrial fibrillation. It is also possible that such rhythm was caused by the atrial lipoma since Crockett and associates[2] have reported a patient with tachycardia for ten years before surgical removal of a large intracavitary right atrial lipoma.

The other postmortem findings in this case stimulate one to consider their possible relationships to the WPW syndrome. The controversy of anomalous AV conduction versus accelerated AV conduction as a mechanism in WPW syndrome has not been settled. The finding of the interatrial "lipoma" with fatty infiltration of the bundle of His and the apparent absence of a bundle of Kent in this case would seem to favor an accelerated conduction mechanism. Prinzmetal has cited multiple examples of acquired WPW syndrome showing changes in the specialized conduction tissue. In these autopsied cases, fibrosis of the AV node was found in patients with myocardial infarction, inflammatory infiltrates in the AV node were found in the case of Chagas' disease, and a fibrocalcific lesion was noted to be distorting the AV node in a case of suspected rheumatic heart disease.

The obstructive hypertrophy within the right outflow tract in this case may also bear a relationship to ventricular pre-excitation. Westlake and associates[3] have reported a family with congenital WPW syndrome in which the affected members develop cardiomegaly in the second and third decades. Analysis of the cases suggests that the WPW syndrome may cause functional subaortic stenosis, leading to hypertrophy of the left ventricle. The pace of cardiac enlargement in these family members appears to depend on the percentage of time pre-excitation replaces normal conduction. It is interesting that Westlake's cases showed type B WPW conduction in contrast to the type A conduction in the present case.

In 1942 Robb and Robb[4] suggested on anatomical grounds that if the deep bulbo-

Table 5. Reports of fatalities in WPW syndrome

Author	Age	Sex	Comment	Reference
1. Wilson, F. N.	not stated		Died during a prolonged attack of tachycardia	Proc. Am. Lif. Ins. Med. Dir. 24:96, 1938
2. Vakil, R. J.	39	F	Mitral stenosis suspected, but not proved. Recurrent paroxysmal tachycardia with CHF. Anomalous AV conduction during tachycardia	Indian Med. Gaz. 77:521, 1942
3. Nielsen, A. L. and associates	not stated		Died of paroxysmal tachycardia with CHF	Nord. Med. 21:450, 1943
4. Wood, F. C. and associates	13	M	Died 2 hr. after tachycardia precipitated while wrestling. Necropsy revealed 3 accessory AV connections	Am. Heart J. 25:454, 1943
5. Ohnell, R. F.	30	F	Died after 12 hr. attack of paroxysmal tachycardia with wide irregular QRS complexes	Acta med. scandinav. (Suppl.) 152, 1944
6. Ohnell, R. F.	20	F	Suddenly died of "functional disturbance" of heart	Acta med. scandinav. (Suppl.) 152, 1944.
7. Kimball, J. L. and Burch, G.	38	F	Increasing episodes of PAT (rate 240)	Ann. Int. Med. 27:239, 1947
8. Kimball, J. L. and Burch, G.	8 mo.	M	Recurrent paroxysmal tachycardia with CHF. Necropsy revealed accessory AV connections bilaterally	Ann. Int. Med. 27:239, 1947
9. Langendorf, R., and associates	33	F	RHD with myocarditis and multivalvular disease. Recurrent A.F. No accessory AV connections found at necropsy	Acta cardiol. 7:24, 1952
10. Silverman, J. J. and Werner, M.	3 mo.	M	Attacks of paroxysmal tachycardia (rate 250–280) with CHF	J. Pediat. 37:765, 1950
11. Rosenbaum, F. F.		M	Patient died suddenly 2 hr. after conversion to NSR from rapid supraventricular tachycardia with persistent anomalous mechanism	Ann. New York Acad. Sc. 65:836, 1958.
12. Vacheron, P.	6 mo.	F	Loud apical murmur, cardiomegaly and WPW conduction noted age 4 mo. Died at home of paroxysmal tachycardia	Arch. Mal. Coeur 47:345, 1954
13. Wolff, L.	55	M	Died suddenly and unexpectedly after 22 yr. of paroxysmal tachycardia. Persistent anomalous conduction noted during tachycardia	Circulation 19:14, 1959
14. Wolff, L.	62	M	First case of Wolff and White. Died suddenly after 37 yr. of episodes of palpitation. Angina present for last 4 yr.	Progr. Cardiovas. Dis. 2:677, 1959/60.
15. Swiderski, J. and associates	14 mos.		Died in PAT. Six attacks in 8 mo.	Brit. Heart J. 24:561, 1962
16. Swiderski, J. and associates	14	M	Ebstein anomaly. Sudden death after swimming	Brit. Heart J. 24:561, 1962.
17. Swiderski, J. and associates	5	F	Ebstein anomaly	Brit. Heart J. 24:561, 1962.
18. Swiderski, J. and associates	16 1	M	Ebstein anomaly, died in CHF	Brit. Heart J. 24:561, 1962.
19. Swiderski, J. and associates	10	M	Primary myocardial disease. Died in chronic heart failure	Brit. Heart J. 24:561, 1962.
20. Swiderski, J. and associates	20	F	Primary myocardial disease. PAT. Died suddenly	Brit. Heart J. 24:561, 1962.
21. Swiderski, J. and associates	15	M	Familial myocardial disease. PAT. Died suddenly	Brit. Heart J. 24:561, 1962

Table I—Cont'd

Author	Age	Sex	Comment	Reference
22. Westlake, R. E.	17	M	Sudden death on playground	Am. Heart J 64:314 1962.
23. Westlake, R. E.	17	F	Sudden death on playground	Am. Heart J 64:314 1962.
24. Westlake, R. E.	30	F	Died of paroxysmal tachycardia during pregnancy. Necropsy revealed subaortic stenosis	Personal communication.
25. Westlake, R. E.	17	M	Sudden death on steps of church	Personal communication.
26. White, P. D.	middle aged	F	Died during paroxysmal tachycardia	Am. J. Cardiol. 17:104 1966.

spiral muscle contracted early it would produce narrowing of the aortic outlet and that this would be equivalent to aortic stenosis. Such premature localized contracting has been demonstrated in the WPW syndrome by Bandiera and Antognetti[7] using roentgenkymography and by Aravanis and associates[8] using cardiac catheterization. Prinzmetal and co-workers[9] demonstrated by high-speed cinematography definite premature contractions of a limited area in the ventricles of dogs in which WPW aberration was produced by subthreshold electrical stimulation of the AV node. The normal sequence of ventricular activation is down the septum to the apex and then up the ventricular musculature to the base. It is reasonable to assume that premature localized activation of the ventricular base should produce hypertrophy of lower muscle fibers over a period of time. Further evidence along this line is the frequent occurrence of WPW conduction in idiopathic hypertrophic subaortic stenosis (IHSS). Four of the 11 initial cases of IHSS reported by Braunwald and associates[10] showed ventricular pre-excitation. Cohen and co-workers[1] reported a series of 29 cases of hypertrophic obstructive cardiomyopathy, three of which showed short P-R interval and QRS complexes suggestive of ventricular pre-excitation. In the large combined series of IHSS reported by Braunwald and associates[11] 27 of 64 such patients had delta waves.

The concept of idiopathic myocardial hypertrophy being an end result of ventricular pre-excitation deserves further exploration. Catheterization studies showing a ventricular systolic pressure drop after normalization of WPW conduction would support this concept. Also, cine angiograms before and after conversion of WPW conduction to normal conduction would be a fruitful study if a change in ventricular contour could be demonstrated. These studies would particularly be indicated in cases of idiopathic hypertrophic subaortic stenosis showing WPW conduction.

The atrial fibrillation noted in this case is a much less common arrhythmia than atrial tachycardia in the pre-excitation syndrome. However, when such rhythm occurs in the setting of WPW conduction it is usually manifested by the abnormally wide ventricular complexes noted in this case. On the other hand, ventricular complexes during paroxysmal atrial tachycardia generally revert to normal conduction and are not of the pre-excitation type. A plausible explanation for the tachycardia in WPW syndrome is the re-entry of impulses conducted retrograde up the anomalous pathway and antegrade down the normal AV pathway with a self perpetuating circus mechanism. It is assumed that the rapid ventricular response in this case is related to antegrade conduction solely along the anomalous route and thus a loss of the protective slowing influence of the AV node. It is noteworthy that the vectors of the ventricular complexes during tachycardia in this case show an extreme rightward orientation as compared to a normal electrical axis during sinus rhythm. On reviewing cases of sudden death in WPW syndrome several are noted with similar aberrant conduction during tachycardia.[12] It is proposed that conduction of supraventricular tachycardia solely along the anomalous pathway constitutes a significant threat to life.

Definite statistics as to the in-

rate hazard related to WPW syndrome cannot be derived from the presently available literature. A total of 22 cases of sudden death attributed to WPW syndrome have been found in the literature (Table I). In addition, four cases (cases 9, 17, 18, and 19 in Table I) are tabulated in which significant organic disease was found to account for death, though WPW conduction could conceivably have played a role. Aetna Life and Casualty[17] has a long term study in 49 patients with WPW syndrome. Four deaths have occurred in 314 patient years. These patients were aged 48, 61, 61, and 63, and their deaths apparently were not directly related to the WPW syndrome. Two of the deaths were due to coronary thrombosis and the causes of death in the other two cases were unknown. Statistical evaluation is pending a longer experience, but this mortality rate appears to be within the predicted normal rate. The medical directors of ten of the larger American life insurance companies[18] were queried regarding rating policies in the pre-excitation syndrome. There was general agreement that the applicant with episodes of paroxysmal tachycardia should be significantly rated (200 per cent mortality rate group to decline depending on age and other factors). On the other hand, the young applicant with the WPW pattern but without previous tachycardia would be given a standard rating by five of the companies and a minimal substandard rating by the other five.

Summary

A case of WPW syndrome with atrial fibrillation resulting in death is presented. Autopsy revealed lipomatous hypertrophy of the interatrial septum, diffuse interstitial myocarditis, and an abnormal muscle bundle within the right ventricular cavity. A possible etiologic relationship of ventricular pre-excitation to myocardial hypertrophy is proposed. The mortality rate hazard of WPW syndrome is discussed.

Appreciation is expressed to Dr. W. Frank Matthews and Dr. William C. Manion for the post-mortem studies on this case.

REFERENCES

1. Widran, J., and Lev, M.: The dissection of the atrio-ventricular node, bundle, and bundle branches of the human heart, Circulation 4:863, 1951.
2. Crockett, J. E., Decker, D., Reed, W., Dunn, M., and Legar, L.: Lipoma of the heart, Am. J. Cardiol. 14:394, 1964.
3. Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. A., Fields, J., and Smith, L. A.: Accelerated conduction. The Wolff-Parkinson-White syndrome and related conditions, Modern Medical Monographs, New York, 1952, Grune & Stratton, Inc.
4. Prinzmetal, M.: The Wolff-Parkinson-White syndrome and related phenomena, Am. J. Med. 12:121, 1952.
5. Westlake, R. E., Cohen, W., and Willis, W. H.: Wolff-Parkinson-White syndrome and familial cardiomegaly, Am. Heart J. 64:314, 1962.
6. Robb, J. S., and Robb, R. C.: The normal heart, anatomy and physiology of the structural units, Am. Heart J. 23:455, 1942.
7. Bandiera, G., and Antognetti, P. F.: Ventricular precontracting area in the Wolff-Parkinson-White syndrome, Circulation 17:225, 1958.
8. Araoutis, C., Lekos, D., Vorides, E., and Michaelides, G.: Wolff-Parkinson-White syndrome. Right ventricular precontracting area proved by cardiac catheterization, Am. J. Cardiol. 13:77, 1964.
9. Scher, A. M.: The sequence of ventricular excitation, Am. Heart J. 8:126, 1960.
10. Braunwald, E., Morrow, A. G., Cornell, W. P., Aygen, M. M., and Hilbish, T. F.: Idiopathic hypertrophic subaortic stenosis, Am. J. Med. 29:924, 1960.
11. Cohen, J., Effat, H., Goodwin, J. F., Oakley, C. M., and Steiner, R. E.: Hypertrophic obstructive cardiomyopathy, Brit. Heart J. 26:16, 1964.
12. Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. S.: Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients, Circulation 30(IV):3, 1964.
13. Vakil, R. J.: A case of mitral stenosis with apparent bundle branch block, short P-R interval, and attacks of paroxysmal tachycardia, Indian Med. Gaz. 77:54, 1942.
14. Ohnell, R. F.: Pre-excitation, cardiac abnormality, Acta med. scandinav. (Suppl.) p. 152, 1944.
15. Rosenbaum, F. F.: Anomalous atrioventricular excitation (panel discussion), Ann. New York Acad. Sc. 65:816, 1958.
16. Wolff, L.: Anomalous atrioventricular excitation (Wolff-Parkinson-White) syndrome, Circulation 19:14, 1959.
17. Alden, J. O.: Medical Director, Life Division, Aetna Life and Casualty. Personal communication.
18. The Connecticut Mutual Life Insurance Company, The Equitable Life Assurance Society of the United States, John Hancock Mutual Life Insurance Company, Massachusetts Mutual Life Insurance Company, Metropolitan Life Insurance Company, The Mutual Life Insurance Company of New York, New York Life Insurance Company, New England Mutual Life Insurance Company, The Penn Mutual Life Insurance Company, and The Prudential Insurance Company of America.

Medical and physiological considerations in the use of artificial cardiac pacing Part II

Edward M McNally M D
Alberto Benchimol M D
La Jolla Calif and
Phoenix Ariz

Pacemakers Techniques and devices

Pacing may be undertaken on either a temporary or a permanent basis While there is little controversy as to the best techn que for temporary pacing there is considerable disag eement as to which of the several currently available devices is the best for permanent pacing

Temporary pac ng

TRANSVEN S There is no question that the t ansvenous technique is the best for temporary pacing In this techn que the st mulat ng electrode located n the tip of a ardiac catheter is placed n either the apex or the outflow tract of the right ventricle and the pace maker un t connected d rectly to the elec trode catheter The pacemaker itself is left externally where both rate and in tensity of stimul can be varied as the need arises Insert ng the transvenous c theter is not d fficult t requires only a fluoroscope and an operator apable of perform ng rigl t heart catheterization nd is done under local anesthesia

The principal hazards of insertion tself perforation f the ventricle and p e cipitation of a ventricular tachyarrhyth mia The latter complication is particu larly l kely to occur in the presence of acute myocardial infarction but s com mon enough in other settings to warrant a defibrillator being held in eadiness during every insertion. The principal later complications of t ansvenous pacing n fection and (late) perforation w ll be discussed below E ther bipolar or un polar electrodes may be used but the bipolar is the easier because ts position is less critical than that of the un pola electrode which must be n contact w th the ventricular wall and because w th the un pola system a ground electrode must be placed elsewhere in the body

The results of temporary pacing w th the transvenous techn que have been qu te satisfactory Pacing can be nst tuted quickly and under local anesthesia and adjustments of the rate or ntensity of the st muli and of electrode position are easily made Perforation and ven tricula tachyarrhythmia are less l kely the more experienced the operator The latter complication c n usually be con

Part [illegible] appeared in the March 1968 issue of the Journal.
From [illegible] and Research Foundation La Jolla, Calif and from the [illegible] Cardiovascular Diseases Good Samaritan Hospital Phoenix, Ariz
Supported in part by grants from United States Public Health Service National Heart Institute Nos [illegible] and [illegible] Arizona Heart Association and Southwest Foundation for Medical Research and Education
Address Scripps Clinic and Research Foundation La Jolla, Calif

trolled by electrical defibrillation and/or antiarrhythmic drugs (which can be used with considerable freedom once the heart rate is under control). Meticulous technique, particularly during repositioning, will reduce the incidence of infection drastically. Any pacemaker which has been inserted in an emergency under possibly unsterile conditions should be assumed contaminated and replaced as soon as possible with another inserted by a different route.

OTHER TEMPORARY DEVICES. In the majority of clinical situations, transvenous pacing can be instituted quickly enough that other methods are unnecessary. Occasionally, however, a transvenous pacemaker is not immediately available or one cannot afford even the short time needed for preparing the insertion of one, as in resuscitation or rapidly recurring Stokes-Adams attacks. In such instances, isoproterenol by continuous intravenous infusion will often achieve control adequate for the brief time required,[illegible] but if this drug cannot be used or is ineffectual, more direct and cruder techniques must be employed.

In unconscious patients, external pacing with electrodes on the chest surface may be used.[illegible] Though this will rarely fail to pace a heart capable of responding to a pacemaker, so painful, exhausting, and distressing are the integumental responses which accompany each stimulus that this technique is virtually confined to resuscitations and other such situations.

Electrodes may also be inserted directly into the myocardium through the skin.[illegible] The risk of puncturing a coronary artery and hemopericardium is small with this technique, and its speed and simplicity, together with the fact that it requires little and inexpensive equipment, makes it the method of choice in emergencies where isoproterenol cannot be used.

Yet another approach is the use of an esophageal electrode in conjunction with an external precordial electrode.[illegible] This approach has not yet been completely explored, but the experience of one of the authors (E. M.) has been that the integumental responses to each stimulus, though far milder than when electrodes are external, are not well tolerated.

Permanent pacemaking. The large number of permanent pacemaker devices available differ from one another (1) in the location of the pacemaker unit (implanted vs. external), (2) in the location of the stimulating electrode (i.e., intracavitary vs. epicardial), (3) in whether the stimuli are delivered continuously at a fixed rate ("asynchronous" pacemaker), continuously at a rate governed by the atrial rate ("synchronous" pacemaker), or (at a fixed rate) only when the spontaneous ventricular rate falls below a preset minimum level ("demand" or "standby" pacemaker).

Pacing failure is a dangerous occurrence, for it not only subjects the patient to the hazards of his underlying disease, but, if abrupt, may lead to prolonged asystole.[illegible] The sine qua non for a permanent pacemaker, therefore—the requirement beside which all other considerations are secondary—is *reliability*. This prime requirement naturally limits the complexity and consequently the flexibility of implanted instruments, as will be emphasized in the following discussion. It should be borne in mind, however, that the restrictions imposed by the need for reliability upon complexity are *relative*, for technology in this area is advancing very quickly, and some of the remarks below concerning them will certainly be obsolete within only a few years.

IMPLANTED VS. EXTERNAL PACEMAKER UNITS. The unquestionable advantages of external over implanted (or buried) pacemaker units is that with the former the rate and intensity of stimuli can be varied according to need and that it can be easily repaired or replaced if defective. Some buried units are adjustable but none easily or reliably so. There are, however, drawbacks to the use of external units, and these have sharply restricted their use.

External Pacemakers. External pacemakers may be coupled to the stimulating electrode either directly, by wires, or by wireless means.[illegible] When the pacemaker is connected by wires to the electrodes, the potential capillary space surrounding the wires as they pass through the skin so predisposes to infection that this ar

rangement cannot be recommended for general use.[11,47,48] It must be said, however, that some workers have maintained many patients for long periods with this method.[47,48]

Infection on this basis does not, of course, occur with wirelessly coupled external units, but these suffer from shortcomings uniquely their own. The first and greatest of these is that the unattached pacemaker unit may be tampered with, broken, displaced out of range, or lost, with a consequent sudden loss of pacing and its attendant hazards. Another problem, reported by those experienced with these units, is the less obvious one that the presence of the external pacemaker serves to remind the patient unceasingly of his dependency upon it, an awareness which has proved intolerable to some patients. Another shortcoming of these units derives from the fact that, since they are coupled to the electrode circuit by radio transmission of one sort or another, the implanted electrode circuit is essentially a radio receiver; this has occasionally led to rather bizarre phenomena, for the electrode circuit can therefore be driven by signals other than those transmitted by the pacemaker, as for example, those produced by electrical appliances or the spark plugs of a running automobile motor.

Despite these shortcomings, however, external wireless pacemaker units offer certain formidable advantages over not only wire-coupled external units, but implanted ones as well. With this device all that must be implanted are electrodes and a receiving circuit, less equipment than with any other device. Miniaturization has already made it possible to combine the receiving circuit and the electrodes into a single unit so small that the entire internal mechanism can be implanted directly on the surface of the heart.[107,84] The advantages of such a device are that it employs no lead wires, whose breakage is still one of the most common causes of pacemaker failure, and that the risk of infection is small because of the relatively little tissue damage produced during its installation. Although we do not feel that at the present time the advantages of external wireless units yet offset their disadvantages, it may well be that in the future they will.

Implanted Pacemakers. Currently the vast majority of permanent pacemaker units are implanted and coupled to the stimulating electrodes by wires. Their disadvantages are clear from the preceding discussion and are, to reiterate briefly, that adjustments of rate[104] or intensity are difficult or impossible, that surgery with its attendant risk of infection is always necessary in correcting pacemaker failure, and that initial implantation surgery is more extensive. Thus far, however, these shortcomings are entirely outweighed by their single overwhelming asset, their *reliability*.

EPICARDIAL VS. INTRACAVITARY ELECTRODE LOCATION. A good deal of controversy exists as to the relative merits of intracavitary (transvenous endocardial) and epicardial electrodes in permanent pacing.[86,87,88] Epicardial electrodes are sutured to the ventricular epicardium and connected by wires to the pacemaker unit, which is implanted subcutaneously either in the anterior abdominal wall or in the axillary or pectoral region.[89] Intracavitary electrodes are located in the tip of a cardiac catheter which is placed in the right ventricle, as in temporary transvenous pacing, and connected to a pacemaker implanted subcutaneously in either the axillary region or elsewhere.[88] The stimulating electrode may be either unipolar or bipolar. If the former is used, the intracavitary electrode must be in contact with the endocardium, and a ground electrode implanted elsewhere. If a bipolar intracavitary electrode is used, on the other hand, contact need not be made with the endocardium,[87] and a separate ground electrode is not needed. The position of a bipolar electrode is thus less critical than that of a unipolar one, and it is, therefore, easier to use.

The main advantage of intracavitary over epicardial electrodes is that the former may be installed under local anesthesia and without thoracotomy, whereas implantation of the latter requires general anesthesia, thoracotomy, and pericardiotomy. Moreover, electrode or wire replacement, still often necessary, can usually be performed easily with intracavitary

devices whereas it requires thoracotomy with epicardial ones These are major advantages in view of the advanced age of most patient with permanent pacemakers, in whom thoracotomy is always undesirable and often not possible There is no question that the availability of intracavitary devices has made permanent pacing possible in many patients who would otherwise have had to do without it Many of the complications which formerly were held to preclude their use have proven less of a problem than expected [17,21] These include thromboembolism infection ventricular perforation and loss of electrode position with failure to pace Thromboembolism has proved rare and anticoagulation unnecessary in most cases Infection occurs no more often with intracavitary than with epicardial electrodes [22] though the former devices are perhaps best not used in patients susceptible to endocarditis.[22] Perforation used to be a fairly frequent problem but with better placement technique and more compliant wire it has become an infrequent one Surprisingly the chief complication of perforation has been not hemopericardium but failure to pace and its solution to withdraw the tip of the electrode catheter back into the right ventricular cavity and re-establish its position [23] Displacement of electrodes *within* the cavity of the right ventricle may also occur and result in failure to pace Failure to pace because of electrode displacement is not uncommon with intracavitary devices and probably is the major drawback in their use it is infrequent with epicardial electrodes. (For a more detailed discussion of endocardial pacing and of uni vs. bipolar electrodes, the reader is referred to these reports. [17,21] [illegible])

We have had no experience with permanent intracavitary pacing but after reviewing the available literature on the subject have concluded that in cases where the risk of thoracotomy is low neither the intracavitary nor the epicardial electrode arrangement is clearly superior and as things currently stand the choice between them should depend principally on the skill and experience of those installing and managing the device In the case of patients in whom the risk of thoracotomy is more than minimal on the other hand there is no question that intracavitary electrodes with an implanted pacemaker is preferable

FIXED RATE VS SYNCHRONOUS PACEMAKERS [illegible] In synchronous pacing the rate at which stimuli are applied to the ventricle is determined by the spontaneous atrial rate. The device detects P waves which then trigger the pacemaker unit to stimulate the ventricle after a controllable delay approximating the physiological P R interval A synchronous pacemaker thus consists of sensing atrial electrodes and stimulating ventricular electrodes connected by wires to a unit which uses the received P wave to trigger the ventricular stimulus after a controllable delay

In order to be safe a synchronous pacemaker must embody two properties of AV conducting tissue that of blocking impulses coming too quickly from the atrium and that of spontaneously generating impulses of its own (escaping) should atrial activity cease. The first property prevents undesirably rapid ventricular beating in response to a fast sinus or supraventricular paroxysmal tachycardia or atrial flutter and the second assures that the ventricle will continue to be paced at an acceptable rate in the presence of atrial asystole low amplitude atrial fibrillation or instrumental failure of the sensing device all of which are interpreted by the pacemaker as absent atrial activity

Synchronous pacemakers thus develop block when the atrial rate exceeds an upper threshold of usually between 110 and 120 per minute but can be otherwise adjusted in manufacture The degree of block is 2 1 at threshold and 3 1 4 1 etc at various higher rates. Conduction ratios between 1 1 and 2 1 analogous to Wenckebach periods, are not currently feasible for technological reasons. A consequence of this is that when the atrial rate rises to and then beyond the threshold the rate falls precipitously as and 2 1 block sets in The pacemaker is also set to discharge at a preset minimum rate usually about 60 if the atrial rate falls below this level or if no atrial activity is detected that is, it escapes [illegible] It is

triggered at a rate less than its lower threshold.

Patients subject to attacks of paroxysmal supraventricular tachycardia with atrial flutter or fibrillation or who are likely to develop these disturbances, are not candidates for synchronous pacemakers. In atrial fibrillation the synchronous pacemaker may respond in either of two ways, depending on the sensitivity of the detecting electrode and the amplitude of the fibrillatory waves. If atrial activity is detected by the pacemaker the ventricles will usually be driven at an irregular rate about 10 beats above the threshold (i.e. minimum) rate for ordinary atrial activity. If not the ventricle will be stimulated at the escape rate of the pacemaker. In critical circumstances there may be alteration between the two.

The sensing and blocking circuits add to both the bulk and the electronic complexity of these as compared with fixed rate units: there are more leads and wires to install and to break, and more circuitry to implant and fail. The consequent loss of reliability must be weighed against the advantages of synchronous or fixed rate units.

In principle synchronous pacemakers offer three advantages over fixed rate ones. They allow the ventricular rate to vary with bodily requirements for cardiac output; they do not give rise to parasystol

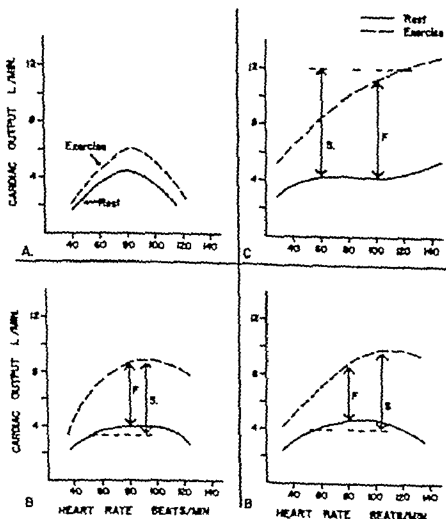


Fig. 2 Resting and exercise ... (see text). F, fixed; S, synchronous.

if AV condu tion should resume and they coordinate tr al stole with ventricular diastole pr serving the atrial contri bution t ntricular filling

Th l l a in which the normal heart varies t utput is by varying its rate changes n tr ke volume play a secondary r l und r n st conditions. By contrast the h rt hose r t s fixed an vary its output l l arying its stroke volume Though troke olume is quite flexible it has l mits and these ay impose upon the fixed rate heart a maximum cardiac out put smaller than t would be capable of at higher rates. A fixed rate may thus restrict the performance of a heart beyond th l its imposed by its *myocardial* capa l lities this is nearly always the case with t l rates below 50.[11] For these reasons, it would seem that a variable rate, that synchronous pacemaker would offer decided hemodynamic advantages over one of fixed rate However as we shall see, thi f r from universally so for in f t rather special conditions must ob t in in order for a patient to benefit from a synchronous pacemaker These are that an appreciably wider range of output actually occur with a variable than with fixed ventricular rate and assuming at this is so that the atrial rate in a va iet of circumstances correspond roughly to the ventricular rate appropriate in those same circumstances. Whether the former requ rement is met can be learned only in hemodynamic studies performed while the temporary pacemaker is in place from which resting and exercise rate-output curves are determined Three general types of curves (*A* *B B* and *C* in Fig 2) have been found in patients with heart block.[1, 11, 12] If it is demonstrated that a variable rate provides a greater range of output than a fixed one it must then be shown that this (variable) ven tricular rate is best determined by the rate of the sinus node To assume without testing the latter is to attribute to the node a wisdom which it often does not possess particularly in the elderly whose sinus rates are frequently to the contrary quite inappropriate How these principles may be incorporated into a systematic approach to deciding whether a syn chronous pacemaker should be implanted will be illustrated in the following ex amples.

In the patient showing rate-output curves of Type *A* in Fig 2 there is a very narrow range of rates at which output is optimal and outside of which it falls off sharply The maximum output is de cidedly subnormal and exercise does not increase the output appreciably over rest ing levels at any rate Severe *myocardial* disease is clearly present. In such a case a synchronous pacemaker would not only be useless it would be a liability Patients showing this kind of curve should have a fixed rate pacemaker installed set at the rate yielding the maximum output About half of all patients with high-grade AV block show curves of this type.[11]

Curve *C* of Fig 2 represents a normal or near normal rate-output relationship the resting output is largely independent of rate save at the extremes of brady and tachycardia and the exercise output is rate-dependent over a fairly wide range of rates, although a fixed rate device set at about 100 to 110 will provide a range of output almost as wide and a maximum output almost as great as a synchronous pacemaker set between 60 and 120 (*F* vs. *S* in Fig 2) The former would not be *feasible* because of the subjective un pleasantness and the inefficiency of an unremitting tachycardia of this rate In a case showing curves of this kind if it can be further shown that the atrial rate corresponds to the appropriate ventricular rate under most exercise and resting conditions, that is, ranges between about 60 and 120 a synchronous pacemaker would be ideal and should be employed

The majority of patients requiring pacemakers show curves intermediate between *A* and *B* and these require more elaborate study What must first be learned is whether the maximum exercise output attainable at any rate is appreciably greater than that occurring at some fixed rate at which the patient might feasibly be paced If this is not so, synchronous pacing should not be selected for it will provide no greater range of output than fixed rate pacing

In Fig 2 *B* for example the maximum exercise output occurs at a rate of 90 and th s output which approximates the maxi

mum which would occur with variable rate pacing does not greatly exceed the exercise output at 80 the fastest rate—we shall assume—at which the patient might feasibly be fixedly paced The range of output which would be provided by variable rate pacing (*S*) moreover is not significantly wider than the range which would occur with fixed rate pacing at 80 (*F*) A synchronous pacemaker would offer little hemodynamic advantage in such a case In Fig 1,*B* however the maximum exercise output occurs at a ventricular rate of about 105 and is substantially greater than the exercise output at 80 the fastest rate—we again assume—at which the patient might be fixed-paced In this case a synchronous pacemaker set between 60 and 110 can be expected to yield an appreciably greater range of output (*S*) than a fixed rate one set at 80 F Before deciding in favor of the synchronous device however it must still be shown that the atrial rate is appropriate in that over the expected range of exercise and resting conditions it varies as the ventricular rate should between 60 and about 105 to 110 If it were found that the atrial rate averaged 90 at rest a synchronous pacemaker would offer little advantage over a fixed rate one set at 80 If the atrial rate regularly rose to beyond 110 with effort a synchronous device would not only be of no advantage but actually a liability for as soon as the atrial range exceeded 110 the ventricular rate would drop precipitously from 110 to 60 and the output fall just as it was needed. In this case too a fixed rate pacemaker set at 80 would be preferable.

Thus, not every patient needing a pacemaker will benefit from a synchronous one—the majority in fact will probably not—and in most cases only hemodynamic study during temporary pacing will allow the decision to be properly made

The fact that the synchronous pacemaker cannot cause ventricular parasystole in the event of recovery of AV conduction may be a formidable advantage The question of whether stimuli falling in the vulnerable phase of the ventricle can in fact induce ventricular tachyarrhythmia is discussed in some detail elsewhere suffice it to say here that there have been enough reports that it does, particularly in the ischemic heart to justify considerably efforts to avoid parasystole It should however be emphasized that there are means other than synchronous pacing of avoiding parasystole (see below)

The third advantage of synchronous over fixed rate pacemakers is that by coordinating hemodynamic atrial systole and ventricular filling they permit better ventricular performance The studies showing this, however have been all acute, which limits their applicability to the long term steady state conditions which obtain in permanent pacing It is our feeling that in most patients the advantage offered by synchrony in this regard is small

In summary the physiological advantages offered by synchronous over fixed rate pacemakers are considerably less weighty than they appear at first glance. On physiological grounds alone only a minority of patients requiring permanent pacemakers fulfill the rather stringent conditions which must be present in order for synchronous pacing to be advantageous. These patients can be identified only by hemodynamic studies performed while they are being temporarily paced Against these advantages must be weighed the disadvantages of synchronous units their greater liability to failure and their blocking properties, which may lead to ill timed and precipitous drops in ventricular rate as the atrial rate rises with exertion or excitement. In only a fraction of cases will the balance favor installation of a synchronous pacemaker

DEMAND PACEMAKERS One of the principal shortcomings of fixed rate pacemakers is that, in the event that AV conduction resumes, they give rise to parasystole with its attendant inefficiency and its small but important risk of ventricular tachyarrhythmia (see above) Parasystole is most likely to occur of course in intermittent forms of block but has proved a problem also in cases of apparently permanent complete block for prolonged survival made possible by pacing has revealed that at least partial recovery takes place in many of these Parasystole does not occur with a synchronous pacemaker

(unless ventricular fibrillation should supervene and convert it into a fixed rate pacemaker) but in most cases the dangers of parasystole are not great enough to warrant implanting one where it would be otherwise undesirable. A device having the advantages (in this connection) of a synchronous pacemaker without its limitations is one which would pace when the spontaneous rate fell below a predetermined minimum (e.g., with the appearance of block) and stop pacing when it exceeded it (i.e., when conduction resumed). Such is the definition of a "demand" or "standby"[11] pacemaker.

A demand pacemaker must include in its circuitry, in addition to a pulse generator, means of sensing the spontaneous ventricular rate and of using this information to instruct the pacemaker itself when and when not to pace. It must therefore be considerably more complex than a fixed rate pacemaker and of about the same order of complexity as a synchronous one. It is simpler than the latter, however, in that its stimulating and sensing electrodes may be the same and that they may both be intracavitary, thus permitting its use without thoracotomy.

There are two kinds of demand pacemakers. One consists of a fixed rate pacemaker whose discharges are suppressed and timetable rescheduled by sensed QRS's occurring at more than a given frequency. The other consists essentially of a synchronous pacemaker whose sensing electrode is ventricular rather than atrial and whose delay is very short; the stimulus is triggered by the QRS (rather than the P) and is delivered into the absolute refractory phase of that same QRS, thus evoking no response; when the ventricular rate falls below the preset "escape" rate of the pacemaker, stimuli are delivered to the ventricle at that rate.

The drawbacks of demand pacemakers are their size and relative unreliability due to their electronic complexity. These shortcomings are thus technological and therefore soluble and it will not be long before demand pacemakers as compact and reliable as fixed rate ones are available; they will almost certainly render fixed rate pacemakers obsolete.

Pacemakers in the future. It seems possible, in the light of present trends, to predict the types of pacemakers which will be used in the future.

It is probable that batteries will be abandoned in favor of an endogenous source of power such as body heat or the mechanical energy of the heart. This will obviate battery failure and in so doing the single most important reason for exteriorizing pacemakers. The trend will be away from devices requiring thoracotomy for their installation and intracavitary ones will probably be employed almost exclusively. As synchronous and demand pacemakers become more compact and *reliable*, fixed rate pacemakers will become obsolete. The choice between a synchronous and demand pacemaker will be made on the basis of hemodynamic studies in each patient during temporary pacing.

Complications of artificial pacing[9, 122, 78]

Most of the important complications of pacing have already been discussed in connection with specific topics. They are of two kinds: those which give rise directly to electrophysiological problems and those which do not. The former include failure to pace and ventricular parasystole and will be discussed below in some detail and the latter infection, erosion of the pacemaker through the skin, and perforation of the heart by the electrode.

Infection occurred prohibitively often with wire-coupled external pacemakers but is very infrequent with completely buried units. Erosion of the pacemaker unit through the skin due to (sterile) pressure necrosis occurs mainly in very thin patients and with chest wall implantations. The use of retropectoral installations has greatly decreased the frequency of this complication and increasing miniaturization will reduce it to negligible proportions. Perforation,[77, 124] which occurs only with intracavitary electrodes, is most likely to happen during or within the first 48 hours of installation and is uncommon with experienced operators employing the newer, more compliant lead and electrodes. Shrinkage of the heart upon the institution of pacing may play an important role in perforation. At the latter

rate both the end-systolic and end-diastolic volume usually decrease and this may cause an electrode wedged in the apex—particularly if it and its leads are stiff—to perforate or one in the outflow tract to advance to the pulmonary artery It is, therefore wise before implanting the permanent pacemaker to provide a period of temporary pacing in which shrinkage can occur During this interval the pacemaker should be carefully watched for displacement and adjustments in its position made as necessary The most common adverse consequence of perforation is failure to pace but it may also lead to mechanical problems, the most important of which is hemopericardium

In earlier pacemaker units battery exhaustion was often accompanied by an acceleration of the rate of stimulation sometimes extreme the so-called runaway pacemaker This does not occur with modern units in which the rate rises only slightly and in these an acceleration in rate is more likely to be due to component failure or a short circuit.[128, 82]

Failure to pace Failure of the pacemaker to pace the heart may result from a decrease in stimulus strength loss of proximity between the stimulating electrode and responsive myocardium or a fall in the rate of stimulation to levels lower than that of the spontaneous pacemaker which are in turn due to battery exhaustion component failure short circuits within the unit wire breakage dislodgement of an epicardial electrode or displacement of an intracavitary one increased impedance between electrode and myocardium (usually due to infection) or an increase in the threshold of the heart These difficulties are for the most part technical and technological and as skill and materials improve failure to pace has become less and less common

Failure to pace may have three adverse consequences asystole parasystole and leaving the patient with the condition for which he was paced in the first place *Asystole* may follow the abrupt cessation of pacing and the consequence of the artificial pacemaker having depressed the spontaneous one upon whose escape the heart must rely after the loss of artificial pacing The escape interval tends to be proportional to the difference in rate between the artificial and the spontaneous pacemakers and is longest in AV block due to bilateral bundle branch block where the escape pacemaker is located below the bifurcation (see above)[8, 46, 47] *Parasystole* may occur when owing to wire breakage component failure or unstable electrode position stimuli are applied sporadically to the ventricle or the rate of pacing falls. The hazards of parasystole will be discussed separately below Once failure to pace has become a *fait accompli* the patient is exposed to whatever problem led to his being paced initially It may be catastrophic if the problem was Stokes-Adams disease or recurrent ventricular tachyarrhythmia more benign if a chronic slow rate problem of another kind

Ventricular parasystole Should the spontaneous ventricular rate approximate or exceed that of a fixed rate artificial pacemaker the latter invulnerable to the spontaneous beats, becomes a parasystole This usually occurs in intermittent or transient AV block, with the return of conduction but will become an increasingly frequent problem as the indications for pacing are liberalized to include not only high grade AV block but other conditions, in which spontaneous changes in the ventricular rate are more likely It should be borne in mind however that recovery of conduction of some degree has been observed increasingly often in cases initially thought to have complete and irreversible AV block The principal adverse consequences of ventricular parasystole are that it may provoke repetitive response and lead to ventricular tachyarrhythmia and that it may embarrass myocardial performance and efficiency Of these the former though less common than the latter can be the more catastrophic

The parasystolic pacemaker stimulus may evoke repetitive response when it falls into the vulnerable phase of a spontaneous ventricular beat There was formerly some doubt as to whether pacemaker stimuli of normal strength and duration are capable of causing tachyarrhythmia The phenomenon has been unequivocally shown to occur however and that it is

moreover not uncommon is suggested by the far greater incidence of ventricular fibrillation and the higher mortality rate in patients who have a return of conduction than in those who do not.[1, 128] The fibrillation threshold normally so exceeds that of capture that the stimuli of a properly adjusted and functioning modern pacemaker cannot provoke a repetitive response even though they fall into the vulnerable phase should the fibrillation threshold be reduced to levels approaching that of the capture threshold, however, they may. The most common cause of such a depression of the fibrillation threshold is ischemia,[?? ??] and it is in the ischemic heart that pacemaker parasystole is most likely to provoke ventricular tachycardia or fibrillation. This is an important reason for conservatism in the use of pacing in acute diaphragmatic infarction with AV dissociation (see above) for here a lowered fibrillation threshold and the likelihood of parasystole with the resumption of conduction co-exist. The fibrillation threshold is also reduced during the period immediately following the implantation of epicardial electrodes,[1] with the use of sympathomimetic drugs, in digitalis poisoning, and in certain electrolyte derangements.

A less catastrophic but invariable consequence of pacemaker induced ventricular parasystole is the irregular and often inappropriately fast ventricular rate to which it gives rise. In a heart whose rate output curve is narrow and peaked (Fig. 2,4) this may seriously embarrass cardiac performance and in one which is marginally ischemic lead to inefficiency sufficient to cause angina or yet graver ischemic complications.

Parasystole does not occur with the demand pacemaker and this is one of the principal reasons why the latter will no doubt soon supersede the fixed-rate pacemaker. Atrial pacing also avoids (Fig. 2) ventricular—though not atrial—parasystole, and this mode of pacing should be given consideration when the problem is other than AV block and when the likelihood of atrial tachyarrhythmia is small as, for example, in suppressive pacing, sinus bradycardia, and SA block. Synchronous pacing avoids ventricular parasystole but not all of its dangers. Should ventricular premature beats occur and fail to discharge the atrium, the next P wave will trigger a stimulus which may fall within the vulnerable phase of the premature. Repetitive firing during synchronous pacing has been reported.

Coupled and paired pacing—special uses of pacing[134-140]

Of the less common uses of cardiac pacing, the most interesting and most important is coupled and paired pacing. The principle underlying these two techniques is essentially the same and consists of using a pacemaker to induce a continuous artificial bigeminy of either the atrium or the ventricle in which the second (premature) beat of each bigeminal couplet is so closely linked to the first (fundamental) that it gives rise either to no ventricular contraction (atrial pacing) or to one of negligible magnitude (ventricular pacing). The latter phenomenon, whereby a double *electrical* rhythm produces a single *mechanical* rhythm at half the pacemaker induced electrical rate, is the key to these techniques. How this is achieved varies according to whether the atrium or the ventricle is employed as the pacing site. When the atrium is used, the premature beats are introduced so soon after the fundamental beats that they encounter still refractory AV conducting tissue, fail to reach the ventricles, and therefore evoke no ventricular response, either electrical or mechanical[??] (Fig. 3,*A*, *B*, and *C*). When the ventricle is the pacing site, on the other hand, ventricular bigeminy is produced (Fig. 3,*D* and *E* and Fig. 4), but the premature beats occur so early as to evoke a mechanical contraction of negligible magnitude which blends indiscernibly with that of the previous fundamental beat (Fig. 5).[??] The latter phenomenon is possible because mechanical refractoriness persists slightly longer than electrical refractoriness.

Coupled or paired pacing of the atrium then results in atrial bigeminy which, since the atrial premature beats are not conducted, is associated with a single ventricular rhythm at half the atrial rate (Fig. 2,*A*, *B*, and *C*).[?] Coupled or

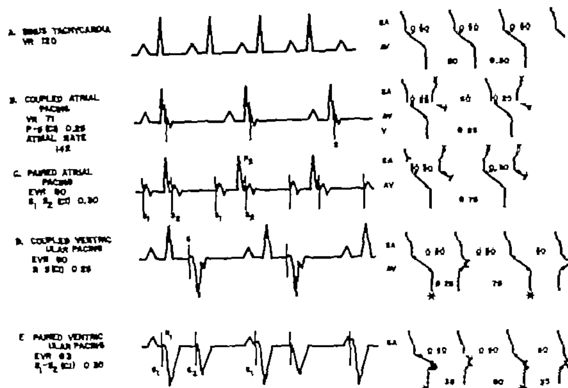


Fig. 3. *A*, Sinus tachycardia. Rate = 120 per minute. *B*, Slowing of *A* by coupled atrial pacing. Nonconducted pacemaker-induced atrial premature beat depolarizes sinus node pacemaker delaying appearance of next sinus discharge by 0.35 sec. This delay in ventricular excitation 0.35 sec. decreases ventricular rate to about 71 per minute. Ventricular rhythm electrically and mechanically single. *C*, Slowing of *A* by paired atrial pacing. Long interval (S_2-S_1) between pacemaker stimuli insures continuous suppression of sinus node pacemaker. Ventricular rate electrically and mechanically single. *D*, Slowing of *A* by coupled ventricular pacing. (Pacemaker-induced ventricular premature beats do not elicit ventricular contraction.) The artificial prematures, since they do not reach sinus node, do not upset the latter's intrinsic discharge rate, but do block conduction of alternate P waves to the ventricle, thus reducing effective the ventricular rate to half the atrial. Note that this same rate reduction would occur with a variety of coupling intervals. Ventricular rate electrically bigeminal, mechanically single. *E*, Slowing of *A* by paired ventricular pacing. Note that, since the long pacemaker interval exceeds 0.50 sec., the sinus rate, interference by the atrium will occur intermittently. Ventricular rate electrically bigeminal, mechanically single. Abbreviations: *P*, Sinus-induced P waves; *p*, pacemaker-induced P waves; S_1, pacemaker stimulus; S_1, first of pair of pacemaker stimuli in paired pacing (fundamental stimulus); S_2, second of pair of pacemaker stimuli (premature stimulus); *VR*, ventricular rate. Mechanically effective ventricular beats. *CI*, Coupling interval. *EVR*, effective ventricular rate. (In rhythm diagrams: *S*, sinus node; *SA*, sinoatrial conduction; *A*, atrium; *AV*, atrioventricular conduction; *V*, ventricle.)

paired pacing of the ventricle produces ventricular bigeminy which since the ventricular premature beats evoke virtually no ventricular contraction is associated with a *mechanically* single ventricular rhythm at half the electrical ventricular rate.[10, 8-10] Thus, in both atrial and ventricular coupled or paired pacing the mechanically effective ventricular rate is half that of the pacemaker-induced bigeminal one and equal to the fundamental one. Two very important differences between the atrial and the ventricular techniques derive from the fact that in the latter the ventricular rhythm is electrically single and in the former electrically bigeminal. The first is that the risk of ventricular fibrillation is associated with ventricular pacing but not with atrial and the second is that potentiation" inevitably accompanies ventricular but not atrial pacing.

The risk of fibrillation in ventricular pacing results from the fact that the premature beats, in order to evoke only insignificant contractions, must follow the previous beat so closely as to fall in or very near the vulnerable phase.[10,37] In the

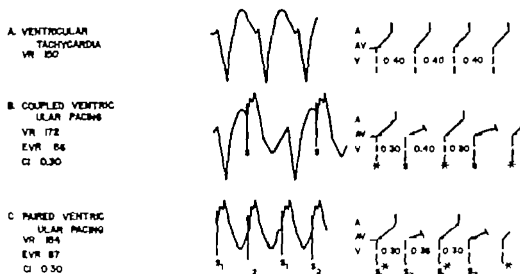


Fig. 4. Coupled and paired ventricular pacing (see text).

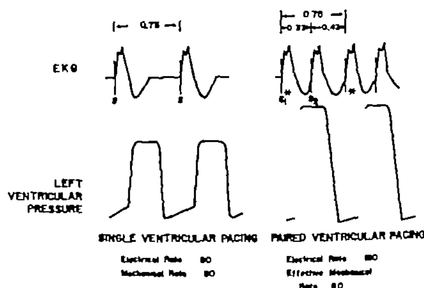


Fig. 5. Diagram illustrating the effect of single and paired ventricular pacing on the left ventricular systolic and diastolic pressures (see text).

healthy heart this carries little risk for the fibrillation threshold is many times stimulus strength but in the diseased—and particularly the ischemic—heart the fibrillation threshold is much reduced[11,14] and the risk of provoking a repetitive response is substantial.[14] This risk does not exist of course with atrial pacing. The latter does, however, carry the risk of inducing atrial flutter or fibrillation.[15]

Potentiation refers to changes in ventricular contraction which occur with coupled or paired pacing of the ventricle. The phenomenon is best illustrated by the following experiment (Fig. 5). If the ventricle is paced at a given rate with single stimuli and then with paired stimuli at the same fundamental rate (the effective mechanical rate remaining therefore the same), a ventricular pressure tracing will reveal that the maximal developed pressure and the rate of rise of pressure

is greater with paired than with single pacing and that the end-diastolic pressure, if high during single pacing falls with paired pacing (Fig 5)[141 *] These changes in the character of myocardial contraction which also occur in isolated heart muscle strips[141,144] have been called augmentation[134,144] or extrasystolic potentiation[139,144] Potentiation is a sustained steady state phenomenon and is of appreciable magnitude for the maximal intraventricular pressure may more than double and dramatic decreases in end-diastolic pressure occur * It is not however always accompanied by an increase in the cardiac output even in the presence of heart failure.[134 140 18] There is associated with augmentation an increase in the myocardial stroke oxygen requirement which occurs regardless of whether cardiac output rises and which is substantial averaging 35 per cent[149] Augmentation usually results in an increase in coronary flow but whether this will balance the increase in the myocardial need for oxygen is in each case unpredictable How closely coupled extrasystoles augment contractility is unknown[141 137 144] but the effect probably relates to an enrichment of calcium at the inner surface of the membrane due to the relative increase in the time during which the membrane is in the depolarized state.[44]

The fundamental rhythm to which the premature extrasystoles are linked may be either the patient's own or itself pacemaker-induced To the former case the term coupled pacing is applied and to the latter paired pacing In coupled pacing[81,144] the R wave is used to trigger the stimulus, which is applied after a controllable delay the *coupling interval* A coupling pacemaker consisting then of a sensing device a delay circuit and a stimulator is essentially a synchronous pacemaker In paired pacing on the other hand in which the fundamental rhythm is also pacemaker induced the pacemaker is a pulse generator which delivers stimuli at regularly alternating longer and shorter intervals,[189] both of which may be altered independently of the other so that either the fundamental rate or the coupling interval can be varied without changing the other In paired pacing the fundamental rate is held constant by the pacemaker and does not change unless a faster competing spontaneous pacemaker emerges and interferes. In coupled pacing by contrast, the fundamental rate is spontaneous and may therefore vary This is particularly likely to happen if the fundamental rhythm is sinus tachycardia for the ventricular slowing brought about by the coupled pacing may cause hemodynamic changes which in turn may affect the reflexes governing the rate of discharge of the sinus node.

Paired and coupled pacing may be used to slow the mechanical ventricular rate potentiate ventricular contraction suppress ectopic foci or for any combination of these purposes. The proper clinical role of these techniques has yet to be defined however and they must still be considered as experimental

Slowing the ventricular rate[81,141,137 n 1a] Either coupled or paired pacing of either the atrium or ventricle can be used to slow the ventricular rate. The first consideration in deciding which technique to use must be the site of origin of the tachycardia, for though ventricular pacing can slow any kind of tachycardia atrial pacing is capable of slowing only those arising in the atrium

In nodal or ventricular tachycardia therefore choice is limited to paired and coupled ventricular pacing[81] An important difference between these two techniques is that if the tachycardia should terminate this fact will be obscured by paired pacing which as it were will not let the rate drop whereas it will of course be immediately manifest with coupled pacing In some situations this may prove an important advantage of coupled over paired pacing Paired pacing on the other hand offers the advantage of allowing a variable range of effective ventricular rates whereas coupled pacing permits little or no control The effective ventricular rate with coupled pacing moreover since it usually is about half the rate of the tachycardia being treated may prove too slow Whichever technique is chosen the risk of ventricular tachyarrhythmia is assumed and augmentation with its attendant phenomena, accepted The latter may in some instances be a tolerable or even desirable

addition to slowing but in others it may not indeed it altogether may preclude the use of pacing to slow the rate Its use is also precluded in some cases by an inability to avoid repetitive ventricular responses.

In sinus or ectopic atrial tachycardia one may choose any of the four possible techniques. *Atrial pacing is in general* preferable to ventricular—unless potentiation is sought too—because it is less risky In choosing between coupled and paired atrial pacing one must consider that whereas paired pacing fixes the rate coupled pacing allows it to change should a change occur in the underlying spontaneous rate. In sinus tachycardia such an alteration may provide a valuable index of the hemodynamic efficacy of the slowing in that it reflects a change in rate of discharge of the sinus node and in ectopic tachycardia it would signal the termination of the ectopic rhythm Coupled pacing may however produce too-drastic slowing of the ventricular rate and for this reason have to be abandoned for paired pacing with which a wide range of rates is possible. Another problem encountered with coupled atrial pacing is that of sensing P waves, but since R waves are in most instances as suitable as P's for triggering atrial stimuli this should not often preclude the technique [illegible] Should potentiation be sought in addition to slowing ventricular pacing must of course *be used Ventricular pacing and the relative* merits of the paired and coupled techniques have been discussed in connection with nodal and ventricular tachycardia but it should be pointed out here that in atrial tachycardia coupled ventricular pacing is apt to cause too drastic a slowing for since it slows by producing a full compensatory pause it reduces the ventricular rate to half the atrial

One of the most important uses of cardiac pacing may well prove to be in slowing undesirably fast sinus tachycardia This tachyarrhythmia certainly one of the most refractory can in fact be approached directly in no other way There is reason to think that the sinus rate particularly in the elderly is often inappropriately fast in terms of ventricular function. In discussing synchronous pacemakers we have already alluded to experiments performed during temporary pacing in patients with complete AV block in which it was found that many showed narrowly peaked output rate curves with optimal rates under 100 per minute and a rapid fall in output with rate increases beyond the optimal There is no reason to think *that this sort of output-rate* response simply because it was discovered in patients with heart block is peculiar to patients with this conduction disturbance it is far more likely merely a nonspecific manifestation of advanced myocardial disease with grossly curtailed reserve and unrelated to the block per se. It is therefore probable that many elderly patients who run sinus rates over 120 either during acute illnesses such as myocardial infarction or infection or in health with exertion are well beyond their optimal rate in terms of output and myocardial efficiency and on the descending limb of their output rate curves. In such patients, paired or coupled pacing—temporarily with transvenous equipment or permanently with synchronous pacemaker stimulating the atrium—may prove most beneficial

Potentiation [illegible] The proper clinical role of augmentation is as poorly defined as that of coupled and paired pacing in slowing the heart [illegible] The dangers of ventricular fibrillation and of myocardial ischemia have tended to limit *its use to dismal situations where all else* has failed Since these are precisely the circumstances in which it is least likely to be of help and most likely to lead to disaster it cannot be said to have been given a fair trial

Augmentation may be used to increase the cardiac output or to lower the end-diastolic pressure.[illegible] Its efficacy in a given case however depends not only upon whether these ends are achieved but also upon whether the cost to the heart of achieving them can be borne for the increase in myocardial power which is the essence of augmentation increases the oxygen requirement of the heart [illegible] Fortunately augmentation is also accompanied by an increase in coronary flow [illegible] The degree to which it is increased depends in part upon the associated change in rate and the capacity of the coronary tree If

the increased myocardial oxygen requirement brought about by augmentation is not accompanied by a proportional increase in coronary flow myocardial ischemia relative or absolute will result. In some cases augmentation will not lead to ischemia at all and in others, a mild relative ischemia may be a tolerable price if the effects are otherwise beneficial But in most patients with ischemic even a small increase in its degree is not acceptable whatever the benefits otherwise bestowed It should be made clear however that in some patients with myocardial ischemia particularly if the heart rate is fast and the output low augmentation may well result in an increase in coronary flow which will more than offset its energy cost and actually reduce the degree of ischemia

One of the difficulties in assessing the efficacy of augmentation derives from the fact that it is usually accompanied by a change in heart rate which makes it impossible to segregate the effects of the change in rate from those of augmentation per se. Whenever possible therefore both atrial and ventricular pacing at the same rate should be done in order to disentangle the effects of rate from those of augmentation

Augmentation will probably find its greatest usefulness in cases of intrinsically reversible heart failure such as after open heart surgery when the heart cannot be weaned off the pump In shock associated with normal or high central venous pressure after resuscitation where low output persists despite an adequate rhythm and in acute pulmonary edema or cor pulmonale[1??, 17] Where myocardial ischemia is the underlying problem—in acute infarction particularly—the risk of ventricular fibrillation and of further aggravating the ischemia probably will preclude the use of augmentation However until more experience is gained with this technique there should be no hesitation in trying it in refractory situations, whatever the problem In such cases it should be used promptly once the refractoriness of the situation is recognized and not left until all hope for improvement is past

Other uses and techniques Just as ordinary single pacing can be employed to suppress ectopic foci in order to prevent paroxysmal tachycardia, so can paired or coupled pacing[?] The advantage of the latter techniques is that they can achieve the same degree of suppression at lower mechanical ventricular rates Their drawback is that they themselves tend to produce tachyarrhythmias. Too little experience has been thus far reported to comment further on this use of coupled and paired pacing

An interesting variant on paired and coupled pacing and a logical extension of it is triple pacing in which an additional extrasystole is introduced after the premature beat of paired pacing The purpose of this is to produce yet greater slowing of the mechanical rate or to even further suppress ectopic foci A recent report of the successful use of triple pacing in fast ventricular tachycardia illustrates these principles very well.[147]

Summary

This review has been concerned with medical and physiological considerations in the clinical use of cardiac pacing Certain problems were selected for discussion and the relevant pathology and pathophysiology treated in some depth Particular attention was given to the Stokes-Adams syndrome heart block complicating acute myocardial infarction the electrophysiological complications of pacing the appropriate roles of synchronous vis-a vis-fixed-rate pacemakers, and the nature and possible applications of coupled and paired pacing The importance of hemodynamic and electrophysiologic studies during a preliminary period of temporary pacing in establishing the optimal mode and rate of permanent pacing was stressed The review was confined to clinical material and no attempt was made to discuss purely experimental and investigative uses of pacing

We wish to express our deepest gratitude to Dr Richard Langendorf of Chicago for his invaluable detailed review of large [illegible] of this paper We wish also to express our appreciation to Dr Arthur Davison of the Scripps Clinic and to Van Stevens, Teresa Harris, Sandra Jennings, and Joan Buhanan for their technical assistance

REFERENCES

93 Davies, G Harris, A. M Leatham A., Siddons, H and Bluestone, R.: Long term

endocardial pacing for heart-block, Lancet 2:30 1965

94 Lillehei C W Le y M J Bonnabeau, R C l ong D M nd Sellers, R. D Direct ure lec ric l timulation for acute post surg l nd postinfarction complet heart block A New York Acad Sc 111:938, 1964

95 Zoll P M l e thal, A J Norman L R nd Belgard, A H Treatment of Stokes-Ad d se se by external electric stimulation of he heart Circ lation 9:482 1954

96 Levow t B S Ford W B and Sm th, J W The se of direct tim lating myocardial lectrodes complet trove tricula block, J Thoracic & C rdiov Surg 10:283 1960

97 Zoll P M and Line thal A J External elect ic tim lation of the heart Ann New York Ac d Sc 111:932 1964

98 Albert H M Glass, B A nd Levy L Ther py of c omplet trioventricular block mplic t ng recent myocardial infarction, Dis Chest 48:561 1965

99 Roe B B I tractable Stokes-Adam disease m hod of emergency management Am H rt J 69:470 1965

100 M N H F M Meyer F C and Langen d rt R Elect e countershock in unanesthe t zd pa ient th use of a esophageal elec ode Circ lation 33 124 1966

101 Ischia S Peracchia, A Maffei-Faccioli, A Bianchi, P nd F toni, I A. Studio dei par met elettrici della stimolazione cardiaca effettuata on elettrodosonda endoesofagea en portatori d blocco atrio-ventricolare sperimentalement ndotto, Anestesia & Rianimazione 6:399 1965

102 Anagnostopoulos, C F Glenn, W W L, Holcomb, W G d A Heerkeren D W Epicardial adiofrequency cardiac pacemaker mpla t (preliminary report) Circulat n 33 Suppl 99 1966

103 Wadm W D Glenn, W W L Eisenberg L nd M uro, A Radio-frequency cardiac pacemaker A New York Acad Sc 111:992 1964

104 Camm lli, I Pov R Pierachi, G nd De-S int Pierre C Radio-frequency pacemaker th recei er l implanted in the heart Ann New York Acad Sc 111 1007 1964

105 Abrams L D nd Norman J C Experience ith induct oupled cardiac pacem kers, Ann. New York A ad Sc 111 1030, 1964

106. Morrow A C Elect ical tim lation of the heart. Tech ique and in trument for the management f omplet heart block, Am J Med. 3 34 1964

107 Grace W J Kennedy R J Gregory J Conklin, F nd Gianelli, S The e of the permanent subcutaneous intra enous pacemaker in Ad m St kes yndrome Am J C rdiol. 1 121 1966 (Abst)

108. Karlson K E., Carters, A W Krasnow N and Weck ler R. M Elect ical pacing of the heart w th endoc rd l ml mpla ted pacemakers Review f 60 ses A Surg 163 339 1966.

109 Chardack, W M A myocardial electrode for long-term pacem king, A n New York Acad. Sc. 111:893, 1964

110. Lagergren, H Johansson L. Landegren, J nd Edhag O One hundred cases of treat re ts for Adams-Stokes syndrome with permanent intravenous pacemaker J Thoracic & Cardiovas. Surg 50 710, 1965

111 Stephenson S. E. and Brockman, S. K. P re synchrony Ann. New York Acad. Sc 111:907 1964

112. N than, D A., Samet P Center S., nd You Wu, C Long term correction of complete heart block. Clinical nd physiologic studies of new type of implant ble ynchronous pacer Progr Cardiovas. Dis. 6:538, 1964

113 Carlems, E., Johansson L Lagergren, H and Karlof I New method for atrial-triggered pacemaker treatme t without thoracotomy J Thoracic & Cardiovas Surg 50:229 1965.

114 Benchimol, A Cardiac functions during electrical timulations of the heart Effect of exercise nd drugs in patients with permanent pacemakers, Am J Cardiol. 17:27 1966.

115 Benchimol A. Ellis, J G nd Dimond, E G. Hemodynamic consequences of trial nd ventricular pacing in patient ith normal nd abnormal heart Effect of exercise t fixed trial and ventric lar rate Am. J Med 39:911 1965

116 Lemberg L Castella os, A and Berkovits, B. V Pacing on demand in AV block J.A.M.A. 191 12, 1965

117 Parsonnet, V Zucker I R., Gilbert, L., and Myers, G H Clinical use of an implantable standby pacemaker J.A.M.A 196 781 1966.

118. P rsonnet, V Myers, G H Zucker I R., nd Lotman, H : The potentiality of the use of biologic energy as a power source for impla t ble pacemakers, Ann. New York Acad Sc 111:915 1964

119 Anagnostopoulos, C. E., nd Glen W W L Electronic pacemaker of the heart, g strointestinal tract phrenic nerve, bladder nd arotid sinus: Current tat s, Surgery 60:480, 1966

120 Satinsky V Dreifus, L S., Racine I M se H. L., nd Reynolds, L Cardiac pacing by mean f lectrical energy deri ed directly from the heart Surgery 60:600, 1966

121 The impla table pacemaker powered by en tricular contractions Medical news, J A M A 193:Suppl. 48, 1966.

122. Gordon, A J Catheter pacing in complet heart block, J A.M.A. 193 1091 1965.

123 Furman, S Pa sonnet V nd Dack S Complic tions of pacemaker therapy for heart block, Am. J Cardiol. 17:439 1966.

124 Dressler W Jonas, S., nd Rubin, R Observations in patient ith impl ted cardiac pacemakers. IV Repetitive responses t electrical tim li, Am. J Card l. 15:391 1965

125 Ca tella os, A Lemberg L Jude J R., nd Berk its B V Repet ti ring ur ring during ynchronized lectric l tim lation of the heart, J Thoracic & Cardiov s Surg 51:334 1966

126 T vel, M E., and Fisch, C Repetitive ventricular arrhythmia resulting from artificial internal pacemaker Circulation 30:193 1965
127 Fort, M L., and Sharp, J T Perforation of the right ventricle by pacing catheter electrode Two cases of asymptomatic perforation with survival, Am J Cardiol 16:610, 1965
128 Moss, A J and Rivers, R Brief recordings Myocardial perforation by a pacemaker New England J Med 274:263 1966.
129 Nathan, D A., Center S., Pina, R. E Medow A and Keeler W Perforation during indwelling catheter pacing Circulation 33:128, 1966
130. Coster F Mastrovannis, H Nicolaou, N and St Katsareas, P Tachycardia and death due to an artificial pacemaker Ann. Int. Med 63:308, 1965
131 Wisoff B G Gabor G. E and Donoso, E. Pacemaker induced ventricular tachycardia, J A M A. 192:238, 1965
132 MacLean, L D and Phibbs, C M Relative effect of chronic ischemia and myocardial revascularization procedure on the ventricular fibrillation threshold, Circulation Res 8:473 1960
133 Wiggers, C J Wegria, R and Pinera, B The effect of myocardial ischemia on the fibrillation threshold—The mechanism of spontaneous ventricular fibrillation following coronary occlusion, Am J Physiol 131:309 1940
134. Lopez, J F Edelist, A and Katz, L N Reducing heart rate of the dog by electrical stimulation, Circulation Res. 15:414, 1964
135 Cranefield, P F (Chairman) Conference on paired pulse stimulation and postextrasystolic potentiation in the heart, Bull. New York Acad. Med 41:417 1965
136. Braunwald, E Sonnenblick, E H., Ross, J and Frommer P L Editorial Paired electrical stimulation by the heart A physiologic riddle and clinical challenge Circulation 32:677 1965
137 Cranefield, P F Paired pulse stimulation and postextrasystolic potentiation in the heart Progr Cardiovas Dis 8:446, 1966.
138 Braunwald, E Ross, J Frommer P L., Williams, J F Sonnenblick, E. H., and Gault, J H. Clinic observations on paired electrical stimulation of the heart. Effects on ventricular performance and heart rate, Am. J Med. 37 700, 1964
139 Braunwald, N S Gay W A Morrow A G and Braunwald, E Sustained, paired electrical stimuli Slowing of the ventricular rate and augmentation of contractile force, Am. J Cardiol. 14:385 1964.
140 Castle C H and Briggs L S. Hazard of ventricular fibrillation from paired pulse stimulation (T) Circulation 32(Suppl)II-65, 1965
141 Langendorf R and Pick, A Observations on the clinical use of paired electrical stimulation of the heart, Bull. New York Acad Med. 41:535 1965
142 Braunwald, E Ross, J Sonnenblick, E. H Frommer P L Braunwald, N S and Morrow A. C Slowing of heart rate, electroaugmentation of ventricular performance, and increase of myocardial oxygen consumption produced by paired electrical stimulation, Bull New York Acad. Med 41:481 1965
143 Chardack, W M Gage, A A and Dean, D C Slowing of the heart by paired pulse pacemaking Am J Cardiol. 14:374 1964
144 Koch-Weser J Potentiation of myocardial contractility by continual premature extraactions, Circulation Res 18:330, 1966.
145 Ross, J Sonnenblick, E H Kaiser G. A. Frommer P L and Braunwald, E Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired stimuli, Circulation Res 16:332, 1965
146 Cranefield, P F The present status of paired pulse stimulation and post-extrasystolic potentiation in the heart, Bull New York Acad Med 41 736, 1965
147 Bayley T J Double and triple pulse pacemaking in treatment of ventricular tachycardia, Lancet 1:235 1966

Fundamentals of clinical cardiology

Renal arterial hypertension

Albert N. Brest, M.D.
Philadelphia, Pa.

The association of renal disease and arterial hypertension was inferred by Bright 150 years ago, when he described the morphologic relationship between left ventricular hypertrophy and renal disease. It was assumed for some years thereafter that all hypertension was of renal origin. However, the validity of this assumption was questioned subsequently as additional observations indicated that arterial hypertension was common in individuals without evidence of renal disease. A reawakening of interest in hypertension of renal origin developed with the classic experiments of Goldblatt and associates in 1934.[2] He demonstrated that hypertension could be produced experimentally by constricting the renal artery of the dog. Subsequently, it has become apparent that renal arterial hypertension in man closely parallels the experimental hypertension produced by Goldblatt and co-workers in animals. It has become further evident during the past decade that renal arterial hypertension is the most common potentially curable form of diastolic hypertension. Although estimates of its incidence range from 1 to 25 per cent, our own experiences suggest the incidence within the hypertensive population is about 3 per cent.[3]

Anatomy

The renal arteries usually arise laterally from the aorta between the levels of the lower third of the first lumbar vertebra and the upper third of the second, and slightly below the level of origin of the superior mesenteric artery.[4-7] Supernumerary arteries and arteries to ectopic kidneys may arise from any level of the abdominal aorta, from the common external or internal iliac vessels or, rarely, from the hepatic, superior or inferior mesenteric, right colic, or lumbar arteries. Numerous studies have shown that 20 to 30 per cent of kidneys have supernumerary arteries of aortic origin or otherwise that enter the kidney either at the hilus or as polar vessels above or below the hilus.

Usually, before each renal artery reaches the hilus of the kidney, it divides into an anterior and a posterior branch. These anterior and posterior intrahilar vessels then rebranch within the renal sinus and give rise to a variable number of interlobar arteries which spread out around the minor calyces and enter the renal columns between the renal pyramids. The interlobar arteries subsequently subdivide into branches, the arcuate arteries, which give rise in turn to interlobular arteries which reach the cortex and then give rise to the afferent arterioles of the glomeruli. Just before they enter the glomerulus, the afferent arterioles are surrounded by the myo-epithelioid tissue of the juxtaglomerular (JG) apparatus. The efferent arterioles, formed by the confluence of the glomerular

From the Hahnemann Medical College and Hospital, Philadelphia, Pa.

capillaries give rise to an extensive peri tubular plexus of capillaries.

According to Graves, each renal artery gives rise to five primary branches and each of these branches supplies a separate segment of the renal parenchyma. Graves labeled these five segments as follows apical upper middle lower and posterior Although the segmental arteries are subject to variation in their levels of origin from the main renal artery Graves found them usually recognizable in spite of their vari ations. Typically the posterior division of the renal artery gives rise to the posterior and apical segmental arteries, while the upper middle and lower segmental arteries arise from the anterior division However numerous anatomic variations may be encountered and some investigators feel that no single segmental classi fication is acceptable

Since there are essentially no anastomoses between the various branches of the renal artery in the renal parenchyma, these vessels are functional endarteries. Although a modest collateral circulation can be provided to the kidney by various vessels in the adipose capsule of the kidney and along the renal pelvis and ureter these vessels generally do not provide sufficient blood to prevent renal ischemia following partial or complete occlusion of the artery or its branches.

Pathology

In all reported series, atherosclerosis and fibromuscular occlusive processes of the renal artery constitute the overwhelming majority of lesions. Occasionally renovascular hypertension may result from uncommon lesion of the renal artery—such as primary thrombosis, embolism aneurysm arteriovenous fistula, dissecting hematoma compression by tumor or fibrous bands, and trauma.

Atherosclerosis of the renal artery occurs more commonly in men The lesion usually involves the first cm of the main renal artery less commonly the atheromatous process is localized to a main branch Associated atherosclerotic disease is often present elsewhere especially in the extra cranial carotid and coronary arteries. There is also a substantial incidence of significant aneurysmal or occlusive disease or both of the abdominal aorta and of its peripheral branches. The incidence of associated abdominal aortic disease has been reported to be as high as 30 per cent.

The fibromuscular occlusive processes were originally grouped together and labeled fibromuscular hyperplasia. [21] Subsequently these fibrous stenosing lesions have been divided into four subgroups (1) intimal fibroplasia which involves the intima predominantly (2) medial fibroplasia, which involves primarily the media and often is associated with microaneurysms (3) fibromuscular hyperplasia, a lesion of the media marked by jumbling of fibrous tissue and collagen and (4) subadventitial fibroplasia, a disorder involving the area of the media immediately adjacent to and often including the elastica externa. Although commonly localized to the renal arteries these disorders may at times involve other vessels, e.g a counterpart of intimal fibroplasia may be responsible for pulseless disease in the upper extremities. Whereas atheromatous disease often is limited to the orifice and proximal half of the renal artery these fibrous stenosing lesions often extend peripherally beyond the bifurcation of the main renal artery but infrequently involve the orifice of the vessel Fibromuscular dysplasia occurs more commonly in young patients, especially women The genesis of these fibromuscular occlusive processes is unknown.

Pathophysiology

It is generally acknowledged that the renin-angiotensin-aldosterone system is involved at least in part in the pathogenesis of hypertension due to renal artery stenosis. There is abundant experimental evidence to support this relationship In addition equally impressive clinical data has accumulated

Renin is a vasoinert proteolytic enzyme which is released from the JG cells in the wall of the afferent renal arteriol The renin is discharged into the blood stream where it reacts with an α-2 globulin fraction (renin substrate) to form a decapeptide angiotensin I The decapeptide, which is inactive is then converted by a rather ubiquitous converting enzyme to the vasoactive octapeptide angiotensin II Subse-

quently angiotensin II is broken down enzymatically by the angiotensinases present in tissues and plasma.

It is well established that angiotensin II is a potent pressor substance which can significantly elevate the arterial blood pressure.[77] In addition, angiotensin II is the principal and most potent stimulator of aldosterone biosynthesis and secretion by the zona glomerulosa of the adrenal cortex. It appears that the sodium retention mediated by the associated (secondary) aldosteronism plays a contributory role in the pathogenesis of renal arterial hypertension. It is likely that retention of sodium in the arteriolar muscle walls enhances the vasopressor effect of the circulating angiotensinemia.

The regulation of renin release is not fully understood. Two mechanisms have been implicated. The first involves a baroreceptor in the wall of the afferent renal arteriole which evokes renin release in response to a decrease in renal artery blood flow or alterations in pulse wave contour. The second involves a sodium load chemoreceptor in the cells of the macula densa portion of the juxtaglomerular apparatus.

Although the exact role of the renin-angiotensin-aldosterone system in the pathogenesis of renal arterial hypertension is still uncertain, it would appear that this system is undoubtedly operative in many (if not most) instances of renal arterial hypertension, especially when the hypertension is moderate or severe. However, the involvement of this system does not necessarily exclude other factors that may be operative. In this regard, the kidney may play an important role in the control or release of a yet unidentified *vasodepressor* substances, and the elaboration of these latter substances could conceivably be awry in renal arterial hypertension.

Clinical features

It is well established that renal arterial hypertension may mimic essential hypertension and, in many cases, the history does not provide any differential diagnostic clues. Furthermore, a positive or negative family history of hypertension is of no value in separating these groups. It is also noteworthy that the response, or lack of response, to antihypertensive drugs has been of no value in differentiating renovascular from essential hypertension. On the other hand, renal arterial hypertension should be strongly suspected in the following clinical circumstances: onset of hypertension in young or elderly individuals, malignant hypertension, or sudden acceleration of previously benign hypertension.[3] Renal arterial hypertension also should be suspected when there is a history suggesting the possibility of a renovascular accident.

The most helpful clinical sign leading to a diagnosis of renal arterial hypertension is an upper abdominal bruit. The murmur is often but not invariably heard best near the midline in the epigastrium with transmission to the affected (or more severely affected) hypochondrium.[13] However, it is noteworthy that such bruits are heard in no more than 50 per cent of cases. Thus, the absence of a bruit fails to differentiate renal arterial hypertension from other causes of elevated diastolic pressure. Contrariwise, the presence of an upper abdominal bruit does not necessarily signify renal artery disease.

It is well established that when renal artery obstruction is severe, the increased renin release is accompanied by increased aldosterone secretion. As a result of this secondary aldosteronism, hypernatremia and hypokalemia may occur as late manifestations. Thus, several authors have suggested that renal arterial hypertension may simulate primary aldosteronism.[1] However, a full clinical and laboratory investigation will serve to differentiate primary from secondary aldosteronism. Most important in this regard is the finding of increased circulating renin activity in renal arterial hypertension, whereas renin activity is diminished or absent in hypertension due to primary aldosteronism.

Diagnosis

Since the history and physical findings may be fallible, the diagnosis of renal arterial hypertension must depend ultimately on the use of appropriate laboratory procedures.

Intravenous pyelogram. The intravenous pyelogram is a relatively safe and inexpensive procedure which provides a com

parative index of renal mass and kidney function bilaterally. The minute-sequence technique has been especially valuable as a screening procedure. X rays are obtained every minute for five minutes following rapid intravenous njection of opaque medium and then every five minutes for 30 minutes. A satisfactory and equal nephrogram should be obtained within one to two minutes. The three minute film should demonstrate equal filling of the calyces of both kidneys as well as early filling of the renal pelvis. The four and five-minute x-rays provide further verification of abnormalities on either or both sides.

Whitley and associates found one or more of the following intravenous pyelographic alterations in renal artery stenosis (1) disparity in renal length of 1.5 cm or more (2) delay in appearance of contrast med um in the calyceal system (3) non visualization of an ent re kidney or a portion of a kidney (4) differences in concent ation of contrast material n the affected kidney (5) calcification of renal vessels, as seen in arteriovenous fistulas and aneurysms and/or (6) scalloping of the ureter due to increased collateral circulation.

Howard and Connor[3] found abnormal ties in 75 per cent of cases of renovascular hypertension Correa and associates[24] found abnormal pyelograms in 89 per cent of cases. Although the reported incidence of abnorm al pyelographic findings varies, most authors ha e found one or more pyelographic alterations in at least 75 per cent of patients with renal arterial hypertension

Refinement of techniques of ntravenous pyelography has been made in order to increase accuracy in the detection of renovascula hypertension Dehydrated hydrated excretory pyelograpl y and also the pyelogram urea washout test have found several advocates.[n n] Enhanced re bsorption of ater and sodium is a characteristic physiologic sequence of renal ischemia and accordingly it has been lemonstrated that the disparate reabsorption of water on the affected side (vs. the unaffected kidney) can be better ident fied by a water or urea d uresis Similarly the use of hydration nd a mercurial diuretic or mannitol has been employed with the sole purpose of accentuating subtle differences in concentration of contrast material.[n] Neither Brannan and co-workers[n] nor Schreiber and associates[n] found any false negative pyelograms employing these hydrated techniques in their investigations, the urea washout pyelograms correlated well with the split renal function studies and seemed more specific than the radioisotope renogram

Over all intravenous pyelography has proved to be a rewarding screening procedure n the detection of renal arterial hypertension.[n] A dehyd ated minute-sequence study followed by renal load ng and e aluation of the response to this hydration is especially informative and possibly the method of choice

Radioisotope renogram The radioactive I[131] renogram has been employed as a screening procedure for the detection of renovascular hypert nsion since its ntrodu tion in 1956.[n n] The rate of accumu lation and excretion of the radioactive test agent is measured by placing external scint llation detectors ove the posterior aspects of each kidney I[131] orthoiodohippuric acid (Hippuran) has been found more satisfactory than I[131] idopyracet (Diodrast) mainly because of the lesser hepatic a cumulation of H ppuran Hippuran is excreted almost exclusively by the kidneys, being handled in a fashion similar to para am noh ppuric acid and thereby providing a qual tative measu e of renal blood fl w or tubular secretory mass. The procedure can be performed w th as l ttle as 2 or 3 microcuries of radioactive iodine but doses of 25 to 40 microcuries are usually employed.[n n]

A normal trac ng consists of (1) an in tial spike which has no signifi ance other than indicat ng the first ppea ance of t acer in the kidney region ( ) a slower secondary rise which takes to 5 m nutes to acl ieve its maximum height and reflects the relat e renal blood flow and (3) a rapid exponential fall recognized as the excretory or d nage pl ase The three most nportant features of the renal trac ing are the slopes of the second and third segments and the t me required to reach maximum le els. The renogram provides a qual tat v assessment of renal blood flow kidney function and postrenal ex

cretion. Semiquantitative measurements may be obtained by calculating the time of maximum isotope uptake (T_{max}) and the time of fall of the isotope curve to one half maximum uptake ($T_{½}$).

The advantages of radioisotope renography are ease of performance, lack of trauma and hazard to the patient, and immediate availability for interpretation. Furthermore, a repeat tracing can be obtained within 30 minutes if necessary. According to Winter[77] the renogram is 85 per cent accurate in detecting unilateral and bilateral renal disease capable of producing hypertension. It appears that reliability of the test to detect disparate kidney function is enhanced by obtaining tracings at a urine flow rate between 1.5 and 7.0 ml. per minute.[79]

Physiologic factors which alter renogram contour are the state of hydration, prior administration of urographic agents or drugs that depress tubular extraction of Hippuran, and emotional factors.[7] Fluid restriction or the hydropenic state slows the renal turnover of tracer and produces an increase in transit time in the renogram. Renograms performed shortly after intravenous urography show flattened second and third segments due to saturation of tubular transport mechanisms; therefore renograms should not be performed for at least 24 hours following intravenous urography. Sulfonamides and other drugs known to be excreted by tubular mechanisms can alter the renogram in similar fashion. Emotional factors also can adversely affect the renogram.

Although some investigators[78, 81] feel that the test is unreliable in detecting renovascular hypertension, it is our feeling that the renogram is a useful adjunct to intravenous pyelography for diagnostic screening purposes. In addition, it has definite value in the follow-up of patients with renal revascularization procedures.

Split renal clearance studies. In 1953 Howard and co-workers[82] introduced split renal clearance studies as a diagnostic method following the observations that ischemic rat kidneys reabsorb increased amounts of sodium and water. The test involves bilateral ureteral catheterization with analysis of urine volume and content from each kidney. A 50 per cent or greater reduction in urine flow from the affected kidney plus a decrease of 15 per cent or more in sodium concentration constitute a positive Howard test. Although the method gained immediate popularity as a diagnostic procedure, subsequent investigators questioned the reliability of the test.[83, 84] Birchall and associates[85] demonstrated that the affected kidney also excretes increased urinary concentrations of inulin and creatinine. Stamey[86] reported a modification which utilizes an infusion of 8 per cent urea in saline plus antidiuretic hormone to enhance reabsorption of water in the ischemic kidney. Howard and Connor[87] subsequently modified their original technique by combining it with certain features of the Birchall and Stamey modifications. They considered a positive test to be characterized by greatly reduced urinary volume plus a reduction in sodium concentration or increased concentration of creatinine or PAH on the affected side. In our experience, a difference of 50 per cent or more in urine volume together with an increase in urine inulin (or creatinine) concentration on the involved side indicate a dynamic stenosis but the urinary sodium concentration may be decreased, equal, or increased on the affected side in the presence of significant lesions.[88]

Split renal function studies are most useful in determining whether a unilateral lesion of the renal artery is hemodynamically significant in the etiology of the patient's hypertension. In this regard the test is useful in prognosticating which patients will benefit from corrective surgery. Unfortunately, the technical problems and associated morbidity of these tests as well as the lack of uniformity in their interpretation have caused considerable confusion and controversy. Kennedy and associates[79] believe split clearance studies are unnecessary for the routine assessment of renal artery stenosis and should be reserved for patients with equivocal renograms and intravenous pyelography. However, Stamey[6] emphasizes that the decision for surgical intervention in renal artery stenosis should be based upon these tests.

Renal scan and chlormerodrin accumulation test. Since 1959 the intravenous infusion of radioactive mercury labeled (Hg[??] or

Hg[203]) chlormerodrin (Neohydrin) has been used for scintillation scanning of the kidneys. Of 13 labeled mercurial compounds studied by Kessler and co-workers,[41] chlormerodrin achieved the highest concentration in the kidneys.

The major portion of mercury is excreted in a few hours, but radioactivity can remain in the kidneys for several weeks or months. The long term effect on the renal tissue is unknown. Careful mapping of the renal tissue with a photoscanner is performed. The viable renal parenchyma is outlined and nonviable tissue such as tumors, cysts, infarction or atrophy stand out by contrast.

Simple renal scanning as an isolated procedure has not proved to be a satisfactory screening method for the detection of renal arterial hypertension. However, differential measurements of the rate of accumulation of labeled chlormerodrin by each kidney during a 30 to 60 minute period followed by scintillation scanning has been found to be a more reliable screening method.[42] The most reliable criterion by which one kidney could be compared functionally with the other was the ratio of the rate of accumulation of the right kidney relative to that of the left. In 30 out of 34 patients with unilateral renal hypertensive disease the right left ratios were beyond the normal range.[43] Sodee[44] studied 200 hypertensive patients, 14 of whom were found to have unilateral renovascular hypertension. The combination of Hippuran renogram plus mercury-labeled chlormerodrin uptake and scan correlated well with arteriography and surgical findings in their experience.

Renin, angiotensin, and aldosterone determination. Increasing evidence suggests that the renin angiotensin system plays a substantive role in the pathogenesis of renal arterial hypertension. However, the development of methods of measurement of renal pressor substances has been fraught with certain technical difficulties.

Conflicting data have been found in the determination of angiotensin, probably due to the lack of standardization of the various methods. For example, Morris and associates in a study of 136 hypertensive patients found 46 with angiotensin concentrations greater than 5 millimicrograms in unilateral and bilateral renal ischemia, coarctation of the aorta, and acute glomerulonephritis; the other 90 patients with essential or malignant hypertension, essential hypertension with pyelonephritis, primary aldosteronism and pheochromocytoma showed angiotensin levels less than 5 millimicrograms. In contrast, Genest and co-workers[45] as well as Mulrow[46] have obtained dissimilar results in patients with renovascular hypertension.

More widely employed is the measurement of renin activity in peripheral or renal venous blood. As with angiotensin several methods have been devised.[47-49] Veyrat and associates[48] found arterial renin activity within normal levels in patients with benign and severe essential hypertension and in about half of the patients with renal artery stenosis. However, Genest and co-workers[45] reported that measurement of peripheral venous renin activity is consistently useful in predicting the results of surgery for renovascular hypertension and they consider this determination the procedure of choice in assessing the activity of the renin-angiotensin aldosterone system.

The demonstration that the renin angiotensin system can stimulate aldosterone production has provided a further indirect method of assessing renal arterial hypertension. The finding of increased renin activity plus increased aldosterone production is consistent with renal arterial hypertension. In contrast, low or absent renin activity in the presence of increased aldosterone production suggests primary aldosteronism. Unfortunately, until more simple and accurate methods can be developed the usefulness of these studies is limited to major research centers.

Angiotensin infusion test. Kaplan and Silah[50] devised this test based on the assumption that patients with increased endogenous levels of angiotensin will require greater amounts of exogenous angiotensin to obtain a given pressor response. An intravenous angiotensin infusion is given in graded dosage until a 20 mm. Hg elevation in diastolic blood pressure is obtained. Kaplan and Silah[50] found that patients with essential hypertension require less than 6.5 millimicrograms per kilogram of body weight per minute for a positive

pressor response whereas patients with renovascular hypertension require larger amounts to produce a similar effect. Interestingly, patients with chronic renal parenchymal disease have shown a wide variability in their response.[53] Gorno and Kaplan[54] reported a correlated increase in renal pressor substance obtained by direct biopsy with the angiotensin infusion test. However, other investigators have questioned the validity of the test because they were unable to correlate either significant anatomical lesions or renin levels with the angiotensin infusion test.[55,56] At present, it appears that further well controlled studies are necessary to prove or disprove the validity of the angiotensin infusion test and to determine its clinical applicability.

Renal biopsy. Renal biopsy has been used as a guide for detection of renal vascular disease as well as for assessment of renal parenchymal changes which might contraindicate surgical intervention. The tissue specimen obtained by percutaneous needle biopsy is small and although possibly diagnostic, it often proves to be insufficient for the study of the JG apparatus. Hence, open incisional biopsy is generally required to ensure an adequate specimen for diagnostic purposes.

In man, relationships have been found between the granularity of the JG cells, serum sodium levels, and aldosterone secretion. Both in human and experimental hypertension, the JG cell changes are believed to correlate with an increased production and secretion of renin.[4] Use of the fluorescent antibody technique indicates that the source of renin is the JG cell. Boughton and Sommers[60] believe that aside from its value in the diagnosis of renal ischemia, the JG cell count is a practical method of determining whether nephrectomy or arterial reconstructive surgery may be indicated in treating these patients.

Vertes and associates[61,62] contend that bilateral renal biopsy serves as the best guide for final decision regarding surgical intervention. They believe that if the contralateral kidney is affected seriously by arteriolosclerosis, cure of the hypertension is unlikely. On the other hand, Strickler[63] described a case of malignant hypertension secondary to bilateral renal artery obstruction with documented parenchymal small vessel disease in which surgical cure was obtained after bilateral revascularization. At present, most would agree that additional correlation of biopsy findings in renal arterial hypertension is required before a final judgment concerning its exact role in diagnosis and prognosis can be finalized.

Renal angiography. The definitive diagnosis of unilateral or bilateral renal vascular disease ultimately depends upon renal angiography. This procedure may be performed via the translumbar aortographic approach or else a catheter may be threaded into the aorta and followed by direct injection of dye at the level of the renal arteries.[64] Since renal vascular insufficiency may be present despite normal pyelography, differential renal function studies, or radiorenography, renal angiography is recommended whenever the clinical picture suggests the possible occurrence of this lesion. On the other hand, the angiographic demonstration of renal artery stenosis does not mean necessarily that the stenotic lesion is responsible for the patient's hypertension; most investigators have found examples of marked renal artery stenosis in normotensive patients studied for other purposes.[66] Although numerous complications have been described,[67] increasing experiences have indicated that this diagnostic procedure may be consistently performed without fatal or serious complications.

Other studies. Abrams and co-workers[68] have devised another method to detect renal vascular hypertension. They measure the renal venous washout time, which is defined as the total time elapsed from the onset of the injection of contrast medium into the renal vein to its disappearance. Cinerecording is used as a means of obtaining precise measurements of the washout time. Normal values vary between 1.25 and 3 seconds. Values above 3 seconds have been found in renal artery obstruction greater than 50 per cent. The usefulness of this test may also be extended to appraisal of the contralateral kidney, i.e., its involvement by arteriolar disease and hence the feasibility of surgical intervention.

Kiser and co-workers devised the phonorenogram as an ind rect measurement of transmitted renal artery pulsations using a transureteral cardiac phonocath eter The value of this procedure n detecting renovascular hypertension cannot be assessed until further analysis of these studies prove their eliabil ty

Treatment

Renal arterial hypertension may improve with medical (antihypertensive drug) or surgical treatment The decision as to the more appropriate therapy is generally determined by such factors as age of the patient severity of the hypertension extent of accompany ng cardiovascular involvement and the degree of enal functional mpairment.

Medical treatment of renal arterial hypertension should be considered when the hypertension is not severe when the pat ent prefers a medical regimen and when the location of disease is such that nephrectomy is the only feasible su gical therapy.[78] Medical management may also be indicated in those individuals, especially elderly patients with sign ficant extra renal disease such as coronary or cerebrovascular insufficiency In addition, the effectiveness of antihypertensi ve drug therapy also enters nto the decision for medi al versus surgical treatment In this regard it is noteworthy that normotension can be achieved with antihypertensive drugs in at least 50 per cent of patients w th renal arterial hypertension however despite successful blood pressure eduction, renal function may deteriorate because of progress ischemic renal atrophy beyond n area of enal artery stenosis.[71] Thus there is an important need for close observ tion of renal funct on and size among pat ent treated medically even though the blood pressure may be controlled sat factorily

V ious su gical procedures includ ng nephrectomy and revascularization can be used successfully n managing enal rterial hypertension It s generally ag eed that nephrectom should not be performed unless the kidney is irrevocably damaged or its evascularization is technically impossible On th other hand successful renal revasculariz tion can provide improvement or preservation of renal function as well as satisfactory blood pressure reduction

The techniques of renal revascularization are similar to those applied to occlusive lesions elsewhere in the arterial tree. Although numerous variations in technical procedures have been used to restore normal renal arterial circulation the two most common procedures are the bypass graft and patch graft angioplasty.[72] Because of the lengthy linear involvement usually seen with fibromuscular disease patch graft angioplasty is rarely selected for reconstruction in this condition. Arterial bypass is generally preferred in the treatment of fibromuscular disease and many arteriosclerotic lesions particularly when aortic reconstruction is requi ed in addition The graft materials most commonly employed a e kn tted dacron and autogenous saphenous veins. The usual bypass procedures employed are the aorto-renal and the spleno-renal arterial anastomoses. Endarterectomy may be used satisfactorily n some instances of localized arteriosclerotic occlusion in other cases, esection and graft replacement or division and mplantation onto the aorta may be used successfully Endarterectomy techniques a e generally not applicable to fibromuscu lar lesions

About 80 per cent of patients undergoing successful surgery for enal arterial hypertension obtain a significant antihyper tensi e response w th normotension being achieved in about one half of the group.[72]

As a esult of our own surgical experiences, we have divided the postoperative results into four categories (1) Renal artery stenosis w th enal arterial hypertension optimum improvement in blood pressu e is obtained in this group ( ) Generalized arteriosclerosis with enal artery stenosis and enal arterial hypertension the surgical results have been generally gratifying in this group even though less satisfactory than in the former category The less satisfactory su gical prog sis reflects the presence of extensiv and often generalized vascular d sease n these patients, many of whom have impaired renal function in addition to uncontrolled hypertension. (3) Essential hypertension with concomitant renal artery stenosis and renal arterial

hypertension Blood pressure reduction following surgical treatment is never complete in these individuals since the renal arterial hypertension is merely engrafted upon an essential hypertensive process. (4) R al artery stenosis without renal arterial hypertension surgical treatment obviously fails to control the elevated blood pressure in these instances. It is to be anticipated that a comprehensive diagnostic workup will identify and thereby eliminate these patients from any surgical consideration.

Many patients with renal arterial hypertension have significant accompanying renal functional impairment. The degree of renal deterioration depends upon (1) the duration and severity of the arterial stenosis and whether the stenotic involvement is unilateral or bilateral and (2) the degree and duration of hypertension with its deleterious detrimental effect on contralateral kidney function. It is notable that renal function may deteriorate in spite of effective blood pressure control thus emphasizing the need for close observation for progression in severity of the stenosis or deterioration of renal function among patients treated medically. Surgical experiences indicate that significant renal functional improvement may be achieved following successful renal revascularization. The pre renal functional status should be considered as an important indicator of the need for surgical treatment in the management of patients with renal arterial hypertension.

Conclusions

Renal arterial hypertension is a potentially curable form of diastolic hypertension. Although renal angiography provides the most definitive technique available for establishing the anatomic diagnosis other studies are required to establish whether the stenotic arterial lesion is responsible for the patient's hypertension. Either antihypertensive drug therapy or surgery may be employed successfully in the management of renal arterial hypertension.

REFERENCES

1. Bright R. Report of medical cases selected with a view of illustrating the symptoms and cure of diseases by reference to morbid anatomy. London 1827 Orme Brown, and Green.
2. Goldblatt H. Lynch J. Hanzal R. F. and Summerville W. W. Studies on experimental hypertension production of persistent elevation of systolic blood pressure by means of renal ischemia, J. Exper. Med. 59:347, 1934.
3. Goldblatt H. Studies on experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia, Ann. Int. Med. 11:69, 1937.
4. Maxwell, M. H. and Prozan G. B.: Renovascular hypertension, Progr. Cardiovas. Dis. 5:81, 1962.
5. Brest A. N. and Bower R. Renal arterial hypertension. Incidence diagnosis and treatment. Am. J. Cardiol. 17:612, 1966.
6. Hollinshead W. H. Renovascular anatomy, Postgrad. Med. 40:241, 1966.
7. Merklin, R. J. and Michel N. A. The variant renal and suprarenal blood supply with data on the inferior phrenic, ureteral and gonadal arteries. A statistical analysis based on 185 dissections and review of the literature. J. Internat. Coll. Surg. 29:41, 1958.
8. Graves, F. T. The anatomy of the intrarenal arteries and its application to segmental resection of the kidney. Brit. J. Surg. 42:132, 1954.
9. Verma M. Chaturvedi, R. P. and Thakur R. K. Anatomy of renal vascular segment. J. Anat. Soc. India 10:12, 1961.
10. McCormack L. J. Dustan H. P. Gifford, R. W. Jr. Meaney T. F. Stewart B. H. and Kiser W. S. Pathology of renal artery disease. Postgrad. Med. 40:348, 1966.
11. Strong C. G., Boucher R. and Genest J. Renin angiotensin and aldosterone in renovascular disorders, Postgrad. Med. 40:337, 1966.
12. Genest J. Angiotensin aldosterone and human arterial hypertension. Canad. M. A. J. 84:403, 1961.
13. Peart W. S. The functions for renin angiotensin. Recent Progr. Hormone Res. 21:73, 1965.
14. Dustan H. P. and Page I. H. Renal hypertensive aspect. Clinical characteristics, Am. J. Surg. 107:35, 1964.
15. Mc... R. M. H. ... J. J. and Hefer K. H. Stenosing lesions of the renal arteries. Clinical manifestations, Postgrad. Med. 40:337, 1966.
16. Laidlaw J. C. Yendt E. R. Bird C. E. and Gornall, A. G. Hypertension due to renal artery occlusion simulating primary aldosteronism, Canad. M. A. J. 90:321, 1964.
17. Conn J. W. Cohen E. L. and Rovner D. R. Suppression of plasma renin activity in primary aldosteronism, J. A. M. A. 190:213, 1964.
18. Whitley J. W. ... R. L., Quinn, J. S. and Meacham, I. The radiologic diagnosis of renovascular hypertension. Radiology 78:114, 1962.
19. Howard J. E. and Connor T. B. Hypertension produced by unilateral renal disease. Arch. Int. Med. 109:8, 1962.
20. Correa R. J. J. Stewart B. H. and Boblitt

D E I tra enous pyelography as screening test in renal h pertension, Am J Roentgenol 88 1135 1962
21 Amplatz, K T adiographic tests for assessment of renovascular h pertension, Radiology 79:807 1962
22 Bra man, W Birchall, R Batson, H M and Kattredge W F Deh drated-hydrated excretory urograph in the diagnosis of renal rterial h pertension J Urol. 91:26 1964.
23 Schreiber M H Scoles H F Herring, M E and Remmer A R J The py logram-urea ashout test New England J Med 270 1223 1964
24 White H I Excretion of sodium in lation glomerula function in enal function Bradley S F edit T Second Conf Renal F nc ion New York 1950 Josiah Macy J F unda ion p 127
25 Martin J F U graphic diagnosis of renovascular dise se Postgrad Med 40:289 1966
26 Taplin C V Meredi h, O M J Kode H ad Winter C C Radioisotope renogram external test f ndividual kidney function nd upper urin r act p st nc J Lab & Clin Med 48:886 1956
27 Winter C C Clinic l stud f new renal f nction est ad activ Diodr renogr m, J Urol 6 18 1956
28 Wedeen R I I st man, E Levitt M F and Goldst M H The se of I[131] Hippuran renogram in he detection of disparate kidney func on in h pertensive pa ient Circula ion 32:5 1965
29 T plin, C V Rad isot pe renogr ph enovasc la h pertension Postgrad Med 40:301 1966
30 Moses J J Prentiss R J Mose L V Kiser J R Herhard, W F Tighe, W J nd Whitehead F L E alua ion of the radio renogram in h pertension, J U ol 85:679 1961
1 Stokes J M F sendenberg M J and Swhow, H Comparison of method sed t diagnose renal hypertension Arch Surg 87:238 1963
32 Howard, J F Berthrong M D Sloan, R D and Yend L R Relief of malignant hyper ens o b nephrect m f ur patien h unilateral renal lar disease T A Am Phys 66 164 1953
33 M ell M H Reckner R F Winter C C nd Kleema C R Predictiv est to da eri enal h pertension er ical analy t tenat pec ed pa ien Circulation 22 85 1960
34 F man, C B Ma B M H Kaufman J J and Kleem n, C R Differen ial renal function in dia ns f renov l ar h per tension, Cir la ion 24 4 196
35 Birch ll, R B w H M nd Br mnan W C m ibu on w t differential enal udies he diagnosis of enal arter al h perten io th emph si on he lue of U sodium U C ine Am J Med 32 161 1962
36 Stames T A Dia nosis of curabl euni l teral renal h pertension by ureteral atheterization Postgrad Med 29:496 1961
37 Howard, J F and Connor T B Hypertension produced by unilateral renal disease Arch I t Med 109:8 1962
38 Orestl, G Ivim, K Swartz C and Brest, A N Renal function in enal nd enovascular hy pertension, Postgrad Med 40:3 7 1966
39 Kenned A C Luke, R C Briggs J D nd Sterling W B Detection of renovascular hy pertension, Lancet 1963 1963
40. Stames T A Renovascular h perten ion Am J Med 38 579 1965
41 Kessler R H Lozano R and Pitt R F Studies on structur diuretic activ t rela ionships of org ic compound of mercury J Cl I est 36:656 195
42 Reba, R C McMee, J C and Wagner H N J Radiomer ury-labelled hlormerodrin for ere uptake studies and scintillation sc ing of ilater l renal lesion associated th h pertension, Medicine 42:269 1963
43 Sodee, D B The screening of enal hyperten sion during he mercury 19 chlormerodrin uptake tud and scan J U ol 95:315, 1965
44 Morris K F J Robinson, I R and Scheele, C A The rela ionship of angiotensin to enal h pertension, Canad M A J 90:2 2, 1964
45 Genest J Boucher R de Champlain, J Ves R Chretien, M Bir n, P Tremblay C R s P and Cartier P Studies on enin ngioten- em in hypertensive pa ients, C nad M A J 90:263 1964
46 M trow P The le of re in- ngiotensin stem in he h pertension associated with enal scular disease Canad M A J 90:277 1964
47 Boucher R Vevrat R de Champlain J nd Genest J New procedure for measur ment of h man plasma ngiotensin nd enin activit les S, Canad M A J 90:194 1964
48 Helmer O M Renin activit in blood f om patien h h perten ion, Canad M A J 90:221 1964
49 Warrnsk R Demarjian, Y and Hobler S A method f r he determina on f en blood nd some preliminary findings C nad M A J 90:..5 1964
50 Veys t, R de Champlain J Boucher R and Genest J Measuremen f human arter l renin activ ti some ph siologic l nd pa hologic l tes Canad M A J 90 1 1964
1 Trembla C Y Ves R de Champlain J B ucher R Lefebv R Ros J Cartier P od Genes J Criteria or suc ess f surger in renovascular h pertension T A Am Ph sicians 77:207 1964
52 Kaplan N M and Silah J C The angiotensin infusion est New England J Med 271 536, 1964
53 Gan le D F M r m C nd Pierce N F Angiotensin inf sion test, Clin Res 1 126 1965
54 Gr ron, W E and Kaplan, N M Renal pressor material in ar ia h perten n d se ease Am J Med 63 745 1965
55 Fitz, A F A alenca, M nd Kirkendall,

[illegible] W. M. [illegible] infusion test in normal and hypertensive subjects. Clin. Res. 12:206 1965

56. Br[illegible] [illegible] A. [illegible] Angiotensin infusion test, [illegible] 1965

57. [illegible] and Hart[illegible] P. M. The juxta[illegible] and their relationship [illegible] plasma sod[illegible]m and to the zona [illegible] of the adrenal [illegible]. Am. J. [illegible] 34:561 1958

58. Hart[illegible] W. S. and H[illegible] New approaches the study of cardiovascular disease [illegible] h[illegible] pertension and juxta glomerular cell. Fed. Pr. 20:815 1961

59. H[illegible] I. M. Sutherland, L. E. and Hart[illegible] W. S. J[illegible]aglomerular cells the source of re[illegible] further studies [illegible] the fluorescent [illegible] and the effect of passive [illegible]. Canad. M. A. J. 93:163 1964

60. Hough[illegible] R. M. and Sommers, S. C. A new [illegible] of renal hypertension. J. Urol. 89:133 1963

61. [illegible] and G[illegible] J. A. Observation on [illegible] hypertension. The role of renal biopsy [illegible] 22:536 1964

62. [illegible] G[illegible], J. A. and Goldblatt H. [illegible] arteriograph[illegible] renal function [illegible] and renal biopsy in human hypertension. [illegible] England J. Med. 27[illegible]:656, 1964

63. [illegible] G[illegible] J. A. and Goldblatt H. Studies of patients with renal hypertension undergoing [illegible] surgery. New England J. Med. 272:186, 1965

64. Strickler W. [illegible] Surgical [illegible] of [illegible] hypertension [illegible] arenal arteriosclerosis. J.A.M.A. 191:233 1965

65. D[illegible] Renal arteriography. Postgrad Med. 40:320, 1966

66. [illegible] W. R. Clark, M. D. [illegible] J. E. R[illegible] R. [illegible] and Meininger D. E. Angiography of renal are[illegible] including comparative study of renal artery stenoses in patients with and without hypertension. Radiology 78:879 1962.

67. Crawford, E. S., Beall, A. C., Moyer, J. H. and DeBakey M. E. Complications of aortography. Surg. Gynec., & Obst. 104:129 1957

68. Abrams, H. L. Baum, S. and Stamey T.: Renal venous washout time in renovascular hypertension. Radiology 83:597 1964

69. Kiser W. S. Tanenbaum, H. L. and Holland, J. H. The phonorenogram transureteral phonocatheter recording of the renal artery pulse in the diagnosis of renal vascular disease. J. Urol. 92:191 1964

70. Sheps, S. G. and Bernatz, P. F. Hypertension and renal artery stenosis: medical and surgical management. Postgrad. Med. 40:355, 1966

71. Sheps, S. G. Osmundson, P. J. Hu[illegible], J. C. Schirger, A., and Fairbairn, J. F. Hypertension and renal artery stenosis. Serial observations on 54 patients treated medically. Clin. Pharmacol. & Therap. 6:700, 1965

72. DeBakey M. E. Morris, G. C. J. Morgen R. O. Crawford E. S. and Cooley D. A. Lesions of the renal artery: surgical technic and results. Am. J. Surg. 107:84, 1964

73. Morris, G. C., J. and DeBakey M. E. Renal revascularization: long term results. Brest, A. N. and Moyer J. H. ed. Atherosclerotic vascular disease New York, 1967 Appleton Century-Crofts.

74. Bower R., Brest, A. N. and Wolferth C. C., J. Renovascular hypertension. Pennsylvania Med. 69:27 1966.

75. Morris, G. C., J. DeBakey M. E. and Cooley D. A. Surgical treatment of renal failure of renovascular origin. J.A.M.A. 182:609 1962

76. Brest, A. N. Heider C. and Moyer J. H.: Renal functional changes following surgery for renovascular hypertension: preoperative and long term postoperative results. J. Urol. 90:380, 1963

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

Appraisal of clofibrate as a hypolipidemic agent

Bernard A. Sachs, M.D.
New York City, N.Y.

The association between elevated plasma levels of cholesterol and triglycerides and atherosclerosis is now generally accepted. Scores of experimental drugs that have been found highly effective in lowering serum lipids have not been made available for general use because of real or potential dangers. Many of those which have been marketed with Food and Drug Administration approval have not found patient acceptance because of annoying, albeit not dangerous side effects. Similarly, it had been found impossible to alter the dietary habits of large populations, despite the fact that in a number of large-scale studies it has been shown that the lowering of serum cholesterol and triglycerides by dietary means favorably affects the incidence of complications of atherosclerosis such as coronary artery disease. The ideal hypolipidemic agent would be one which effectively lowers serum lipids and lipoproteins, is nontoxic, is easily administered and is free from annoying side effects to the patient. The compound which most closely approximates these criteria is ethyl-α-p-chlorophenoxyisobutyrate (CPIB, Atromid-S, clofibrate) (I 1).

In 196 Thorp and Waring[1] studied a series of aryloxyisobutyric acids in rats for their ability to lower the level of cholesterol and other lipids in serum and liver and found the compound with maximum lipid lowering effect and minimum toxicity to be parachlorophenoxyisobutyric acid and its ethyl ester. They thought that clofibrate augmented a rhythmic endogenous hypocholesteremic mechanism and deduced that androsterone might be the endogenous agent responsible. They administered clofibrate with androsterone orally to rats and found that the combination produced a continuous hypocholesteremic response. Oliver in England and Hellman and associates in the United States demonstrated that the combination of clofibrate and androsterone orally was hypocholesteremic and hypotriglyceridemic in man. Initially, Oliver[2] reported from observations made on six men that the administration of clofibrate alone did not appear to have any significant effect on serum lipids. However, at a symposium held at Imperial Chemical Industries Ltd, Alderley Park, England in June 196 Hellman demonstrated that clofibrate alone possessed all of the hypocholesteremic, hypotriglyceridemic and other properties ascribed to the combination of clofibrate and androsterone. This was soon

From the Endocrine Service, Medical Division, Montefiore Hospital and Medical Center, New York City, N.Y.
*Head of the Endocrine Service.

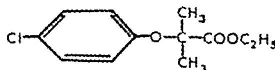


Fig. 1. Ethyl 2-(4-chlorophenoxy) isobutyrate (clofibrate).

[illegible] extended to include more patients by Hellman and associates[4] and confirmed by Oliver and others.

Discussion

Effect on lipids and lipoproteins. The primary effect of clofibrate is to reduce the plasma concentration of triglyceride-rich lipoprotein of very low density (Sf >400). It also reduces plasma concentration of cholesterol-rich low-density lipoproteins (Sf 0-20) to a lesser degree. This results in a reduction of plasma triglyceride levels averaging 30 to 40 per cent and of cholesterol levels averaging 15 to 25 per cent. Associated with this change in low-density lipoproteins is an increase in certain classes of high-density lipoproteins and an increase in the α/β lipoprotein ratio, a decrease in the total exchangeable lipoprotein pool, and a decrease in the catabolic rate of this pool. In addition, lipoprotein lipase activity appears to be increased. As a result of the latter, the height and duration of postprandial lipemia are decreased. Nonesterified fatty acids are not affected. For unknown reasons, about 15 per cent of the patients showed no response to clofibrate administration.

Effects on clotting. In an early study it was observed that requirements for anticoagulants were reduced when clofibrate was administered to patients on anticoagulant therapy. Further investigation disclosed that clofibrate reduces fibrinogen levels, reduces platelet stickiness, prolongs platelet survival,[12] reduces clot lysis time,[13] and prevents the shortening of recalcified clotting time which occurs during postprandial lipemia.

Other effects. Transient elevations in serum glutamic oxalacetic transaminase (SGOT) levels occur in some patients within a few weeks of starting clofibrate[4] and a mild decrease in serum alkaline phosphatase level has been observed. No other abnormalities in liver function have been reported. Rats fed clofibrate in the diet show liver enlargement due in part to an increase in protein and phospholipid.[1, 17] Liver cholesterol and triglycerides are either decreased or unchanged except under special experimental conditions in which triglycerides are increased. Histologic studies of clofibrate-fed rats show a marked increase in the intracellular organelles, lysosomes and mitochondria, which appears to be species-specific. These histologic findings are interpreted as reflecting the metabolic changes within the liver cell produced by the compound. No evidence of liver toxicity in animals or man has been reported.

Clofibrate has been found to produce a reduction in blood uric acid levels. The hypouricemic response is most pronounced in patients with elevated triglyceride and uric acid levels.[19] There is little effect on uric acid levels in subjects without hyperuricemia or hypertriglyceridemia. There is some evidence to suggest that clofibrate has a primary uricosuric effect.

Mechanism of action. The precise mechanism whereby clofibrate reduces plasma levels of triglyceride and cholesterol is unknown at the time of this writing. In Thorp and Waring's original study, the cholesterol-lowering activity of clofibrate appeared to coincide in time with spontaneous reductions in the serum cholesterol of control rats, and they suggested that clofibrate augmented a rhythmic hypocholesteremic mechanism. In view of previous findings of Hellman and associates[20] that thyroid hormone led to increased androsterone and that this androgen metabolite was hypocholesteremic in man, they suggested further that androsterone might be the endogenous agent responsible for the phase changes in cholesterol. They administered clofibrate with androsterone (Atromid) to rats and found that the combination produced a continuous hypocholesteremic response. The hypolipidemic effect of Atromid was confirmed in man soon thereafter.[21] Thorp postulated that clofibrate either displaced androsterone from plasma protein or acted by competing for the binding capacity of serum albumin and plasma acidic compounds and hormones (such as thyroxin), leading to their [illegible]

ration in the liver and a reduction in lipid synthesis.[22]

However, all investigators now agree that oral androsterone contributes nothing to the hypolipidemic effect of clofibrate. Further studies demonstrating the failure of adrenalectomy and gonadectomy to prevent the hypolipidemic effect of clofibrate in rats and man[23] suggest that the mechanism of action is not concerned with potentiation of endogenous steroid hormones. Furthermore, clofibrate has been shown to effectively lower cholesterol levels in thyroidectomized animals, which gives additional evidence that its mode of action probably is not mediated via thyroid hormone metabolism. It also has been shown that inhibition of catecholamine-induced release of fatty acids from adipose tissue is not responsible for the lowering of blood lipids by clofibrate.[24]

The more profound decreases in the triglyceride concentration as compared to cholesterol and the observations that the greatest fall in cholesterol values occur in patients with the highest triglycerides suggest that the primary action may be on triglyceride synthesis. However, free fatty acid turnover and triglyceride production have been found to be normal during clofibrate administration but rates of peripheral clearance of triglyceride in hyperlipemic patients were found to be increased.[25] Others have demonstrated improvement in the fat tolerance test[26, 27] and an increase in fecal excretion of neutral sterols[27] during administration of clofibrate.

Other investigations suggest that clofibrate may act as an inhibitor of cholesterol synthesis. Failure to demonstrate accumulation of desmosterol or other cholesterol precursors tends to rule out inhibition late in the cholesterol biosynthetic cycle. Clofibrate inhibition of acetate incorporation into cholesterol by rat liver slices in vitro has been reported. Avarnoff and colleagues[?] found that the site of inhibition of clofibrate when fed in the diet is between mevalonic acid and isopentyl pyrophosphate, a theoretically ideal site for inhibition of cholesterol synthesis. Other studies by the same author[?] and confirmed by Mishkel and Webb[?] using liver perfusion experiments suggest that the hypolipemic action of clofibrate also may be due to a partial failure of hepatic secretion of triglyceride.

Side effects. Clofibrate administration is virtually free of side effects. There is no known toxicity. Transient nausea and mild diarrhea occur in about 5 per cent of the patients. In some series even these mild side effects were absent.

Contraindications. There are no contraindications to the use of clofibrate. Patients on anticoagulant therapy should be followed carefully with prothrombin time determinations because anticoagulant drug requirements decrease with clofibrate administration.

Clofibrate is supplied in 0.5 gram capsules and the daily dosage is 1.5 or 2 grams depending on body weight. This dosage results in a sustained lowering of plasma lipids and lipoproteins for as long as four years. Associated with the fall in plasma lipids is visible regression of deposits of tissue lipids such as xanthomata and lipemic exudates in the retinae of diabetic patients. One may assume that there is also regression of lipid deposits in the intimae of the coronary and other arteries although of course direct proof is lacking.

In the United States, the Cooperative Coronary Drug Project is utilizing clofibrate as one of the four drugs in a large scale clinical trial to determine whether reduction of plasma lipids favorably influences the incidence of reinfarction or death in patients with ischemic heart disease. Similar cooperative studies with clofibrate are in progress in Britain. Other studies in hyperlipemic subjects without ischemic heart disease have been started to determine whether lowering of plasma lipids by clofibrate rather than diet will reduce the incidence of ischemic heart disease. The next five years should provide firm answers to these questions. Meanwhile, in light of our present knowledge, clofibrate may be considered a safe and effective hypolipidemic agent.

REFERENCES

1. Thorp, J. M., and Waring, W. S.: Modification of metabolism and distribution of lipids by ethyl chlorophenoxyisobutyrate, Nature 194: 948, 1962.
2. Oliver, M. F.: Reduction of serum-lipid and uric acid levels by an orally active androsterone, Lancet 1: 1321, 196_.
3. Hellman, L., Zumoff, B., Kessler, G., Kara[illegible]

R nd t ll ghe I I Reduct on of serum hole 4 m 1 1 ndr terone pr t I Cl I t 41 1 1 196

4 H ll l Z m tt B hessler C hara, I K l l l nd R s nt ld R S Red tion of h se d 1 pid m 1 eth l p hh l he d N l t Med 19 l 3

H M I I ha dver t on m the I 4 ound d d eth l hlorophene s sol s hpid le el J Athero ler Res 3 l 1963

H w t R I M j w I Bl O J nd I R H I ffe d h l hloroph no sol t t h se th d terone m id m m lipid lipoprotei nd n l nd m 1 4 pa me rmal nd h pe l pid l pe J A he ocler Res 3 18 19

7 t m J H The res onse of h perlip s d ems t m I nd h l hle ophenox sol J A he ocler Res 3 115 1963

S mposi m on t om d J Atheroscler Res 3 31 1963

9 Ch M I Rober S D H es D I nd J I Suzma M M nd Bersoh I Effect 4 t mid nd h lchlor phe d t m a t ng fasti ng triglyceride l et I 143 1963

10 C on R C Warle I I nd Spiller C W The ffect of romid n plasm fibrinogen nd heparin est ne J Atheroscler Res 3:615 1963

11 C son I M Donald I Dick nd S Pilk ngt n I D es, B nd I we I Effect of om l pl t let tickiness, J Atheroscler Res 3:619 1963

12 Glynn, M I Murph I A nd Must rd, J I Effec of lobbr t on plat let econom ma I ncet I 447 1967

13 Sri ast a, S C Smith, M J and De ar H A The effect of tromid on fibrinol t act vit of pa ient th schaemic he rt dise se and h perchole ter lemia, Lancet 2:610, 1963

14 M Andrew C M nd I Berton, H W The effect of tromid on the ecalcified plasma clot ting time fter high f t me l Lancet 2:611 1963

15 Azarnoff D I Tucker D R nd Barr G A Studies with ethylchlorophenoxyisobutyrate (clofibrat) Metal olism 14:959 1965

16 Best M M and D nc n, C H Hypolipemia nd hep t omegaly from thylchlorophenoxy sobutyr te (CPIB) in the t, J Lab & Cl Med 64:634 1964

17 M hk I, M A and W bb W I The mechan sm underl ing the hypolipidaemic effect of a romid icotinic acid nd benzmalecene, Bi chem & Pharmacol. 16:597 196

18 Best M M nd Dunc n, C H : Ethyl p chlorophenoxy sobutyr t (CPIB) and liver tri lycerides Circulation 36 II-9 19 7

19 I get C I Experiment l tudies on the t micit of t omid th particular referenc t fine tructur l hanges n li ers of rodents, J Atheroscler Res 3:729 1963

20 Berk w tz D The effect of chlorophenoxyisobutyrat ith nd thout ndrosterone on the serum lipid I t toler nce nd uric acid Metabol sm 14:966, 1965

21 Hellman L Bradlow H Zumoff B Fukush m D K nd Gallagher T F Thyroid ndrogen i terrelation nd the hypocholesteremic effect of ndrosterone J Clin Endocrinol 19:936, 1959

22 Thorp J M A experimental pproach t the problem of disordered lipid metabolism, J Atheroscler Res 3 351 1963

23 Berry C M rsham A Smith L Kellie A E nd Nabarro, J D N The ffect of atromid on the metabolism of adren l teroid nd on plasma l pid fractions, J Atheroscler Res 3 380, 1963

24 D nca C H Best M M nd Robertson, C I A comparison of the effects of ethylchlorophenoxyisobutyrat nd nicotinic acid on plasma free fatty acids, Lancet I 191 1963

25 Ry W C and Sch artz T B Dynamics of plasma triglyceride turnover in man, Metabolism 14 1243, 1965

26 Berkowit D The effect of tromid on serum cholesterol, serum trigly erides, and radioacti fat tolerance l patients ith hyperlipidemia A preliminary report, J Atheroscler Res 3:538, 1963

27 Mit hell, W D, Truswell, A S, and Bronte-Stewart, B : The effect of tromid-S on faecal neutral teroids nd bile acids, Progr Biochem & Pharmacol 2:365 1967

Ethics for the use of live donors in kidney transplantation

When kidney function has ceased, it can be replaced by regular dialysis, or alternatively a healthy kidney can be transplanted to replace the diseased one.

Treatment by repeated dialysis can restore health to patients who would otherwise die, and it would, therefore seem unethical not to provide this when it is needed. However the cost of current methods of dialysis is very high and in no country in the world are sufficient facilities available to provide treatment for all patients who need it. Serious ethical difficulties may arise in deciding to treat certain patients while excluding others.

When a kidney is removed from a healthy individual for the benefit of a sick one, even more serious ethical problems may arise.

The healthy donor has to undergo an operation from which he cannot possibly derive benefit for the sake of another. The donor has to face risks which may shorten his life, and there can be no certainty that the transplant will succeed and in the end his sacrifice may be in vain.

The operation itself entails certain risks including those inseparable from anesthesia. The donor although healthy and presumably well prepared for the operation has to undergo an operation which is more extensive and more potentially injurious than most therapeutic nephrectomies as considerable lengths of blood vessel and ureter must be carefully removed. As far as I am aware, no donor has yet died as a result of the operation, but several have had serious postoperative hemorrhages from the stump of the hilum. Other serious complications in the donor reported by Frankson and associates include pulmonary embolism on the twenty-eighth day and hepatitis in two donors one of whom was on the sick list for 5 months.

The donor of a kidney also has to face unpredictable later risks which may in the long run shorten his life. It is the universal practice to investigate the donor carefully to ensure that he can spare a kidney. ... et al report that 10 of 13 donors investigated postoperatively had lower creatinine clearance than before the nephrectomy. Four of them had raised serum creatinine and ... of them suffered from some degree of renal insufficiency.

There is also the possibility that the donor's life may be shortened if his remaining kidney should later become affected by disease or injury. This possibility is not completely remote as shown by the following experience which I relate.

In October 1962 a 13-year-old woman was admitted to the Renal Unit suffering from terminal renal failure. Her doctor had read of successful transplantation of kidneys between identical twins and believed that she had an identical twin, as was later proved. The patient had generalized anasarca and a blood pressure of 200/110. There was partial detachment of both retinas, which progressed to nearly complete detachment by the following day. The blood urea was 438 mg per 100 ml and marked acidosis was present.

There was considerable clinical and biochemical improvement following vigorous hypotensive therapy and a short dialysis on the artificial kidney.

Her healthy twin was found to resemble her closely and the blood groups were identical in the ABO, Rh genotype, MNS, P, Lewis, Kell, and F groups. The healthy twin was willing to act as donor. Accordingly it was decided to treat the patient by further dialysis to prepare her for transplantation at a later date. Investigation of the healthy sister was planned to ensure that she had two normally functioning kidneys and that the renal vessels were suitable. However shortly after a second short dialysis on the artificial kidney, the patient had convulsions and died.

In January 196– the healthy sister was referred to a urological colleague suffering from urinary incontinence following a cesarean section for her first baby in September 1966. She had not previously had urinary symptoms. She was perfectly normal in every respect except for continual leakage of urine from the vagina. Urinalysis was unremarkable. Intravenous pyelograph showed marked hydronephrosis of the left kidney, the right one being low in position but otherwise normal. Upon vaginal examination urine was seen coming from the vaginal vault through the cervical os. At cystoscopy the bladder was normal but a catheter could not be passed further than 2 cm into the left ureter. At abdominal operation the left ureter was found to be involved in a fibrotic process as it passed the cervix and there was a fistula entering the cervical canal, the distal ureter being normal. The damaged ureteric segment was excised and continuity was re-established leaving a T tube above the anastomosis through a proximal ureterostomy. The distal limb of the T tube became blocked and the abdomen opened again to restore the lumen. Later ... developed because of leakage of

sit of the nost th j rit meum nd the l lomen q ierlag t rres perit ne liz t on of the na on s nd l se Con lesene I the j l l lis d f nars fection h h p dr l t t th t of t If h l l l t l k lne t be ter there es lk l t h kl h l e the left one h h l h bei ed l ould herefore l J h t h h l lee red as lonor he kl l l ja l h k h llness there l l l bei ne kf k lnes t b formed l he ers ll ea h of the reter h l l sed by the esare sect on had l he ght l onl er hes use the left k lne h l been ne l l here l the fact th t th ja ie t h l ri rs fe th rest dfi g sm h h ma recrudesc t g f r the bl l t stene compl tio f llew ng t on is ri ne t W t t l h kt l h th patient not sed k l h lthe gh t the t me th j k l l d not th k h ther ns l d m he se of lent l k l de

l he l ffe l t d wer hi the he lonor t l ll g g k lnes he ta be sol a t l h kler pr ssures mou ng t mor l l l k l f m the member of the f m ly h h l h olu teer gn kidney Th he ha ra t ed his sit iat on

A 28 ld ma h l l th parent b en nd bei he priest 15 of ge At interview b h parent nd he brother expressed will gness t don kidnes f found t be suitable Th mother nd bri her proved iffer in major blo l gro p from the patien h le the f ther goo l ma h Whe the father being i estig ted he ontide l hat he had ne l hed from anesthesi d ring an ppendec om l ri g his outh and he ons nced hat he ould not surv l nother het ll f l it however that h f mil ould never f rg h m if he refused t donat k lnes t his son The situat on complicated l the fact tha his f w Roma Cathol hile he Protesta t nd the h ldren had been bro ght p the Catholi f th ll sa l that his of ould be bes that refusal t donat kidney ould be be cause the son had been brought up t be Ca holics. The only h mane sol tion seemed t pretend t the f ther that his kidnes ere found nsu t ble on pyelography The patient sent for ada erk kidney tra pla t h h succeeded and he is now ell ith normal kidney f nction nd irtually normal biopsy 28 months later

The problem considered al s ha been on cerned w th related donors, here there is tatistic l evidence that the expectation of good result is better than when related donors are used Fre quently no f mily donor allable and many enters ha used unrelated li donors These n related donors have often been the spouse of the recipient. Such donors may ha e strong mot tion for offering kidney from their lose emotional bonds th the patient but often their ch ldren must lso be considered It seems wrong t jeopardize the lif of second parent ithout ny certainty th t the tr nsplant will be success l.

Other nrel ted donors used h Included on t It ha been s id th t onvict convicted of serious imes nd serv long sentences may be helped by l ing llowed t ompensat by giving k lnes Dr St r l however now feel that he made mist k l accepting pri on olu teers nd his experienced iew f th m tter hould be respected

A l l rgument ag inst the of nrelated li donors is th t the result are no better th those d t ned by the se of cada er k lnes

The se f r the use of l e donor t ll rest on the bett results h h ha e f bee achieved be k lnes h been t ken f om h donors. The better result w th l donor be related t factors oncerned w th the org n tion and techn l le of the t splant nd t those concerned th mat hing the tissues of the donor nd rec pient It is nquest on bl sier t t pl t k lnes hen the op rat on be planned l det l in ad nce the p tient properly prepared f oper t on nd the surge l t m ad l le nd ll ncillary services read The kl l bet een the remov l of the kidney nd reimpla t t on is m m l and the k lnes usu ll ommences t f nct on immed t l When the lel longer t m t be hen cada er k lnes re sed, the t nsplant ll nder goes t bul r necr nd does not f nct on for ome time The occurrence of t bul necrosis lthough necessit t ng hal si t support the pa ent until k lnes f nction begi loes not prejudice the ent l result (Williams Wh t and H me 1967) l en hen kidney re t nsplanted bet een indi l als wh nrel ted nd pparentl ll mat hed the oper tion may still f ll for techni l re ons l l ra kson series kidney taken f om li donors nes pro l ced ur ne The author expe rienc ncludes transplant bet een ident l t ins in which the k lnes never produced urine nd n other k l ies t ken from parent donor hich f nc t oned onl brie fl because of aneurysm formation t the sit of the arter l anastomosis Lat f lure of the t pla t may ccu due t recurrence of glomerulonephriti even hen the kidney comes f om identic l t i

The lata from the Kidney Transpl t Registry (1967) show that 55 per cent of the kidne from rel ted donors f nction t one yea compared ith 21 t 33 per ent (accord ng t hether local irradia t on of the graft used or not) from unrel ted living donors nd cada rs. The figures are some hat mproved hen recent experience onl is considered, and f t anspla ts carried out since J nuary 1965 the estimated per cent survival t one yea for li donors is 65 nd for ad er donors is 39

Consider bly better result ith ad eric trans pla t are obtained l some centers, presum bly beca se these centers ha pplied themsel to the sol tion of the special problem sociated ith the use of this sourc of kidneys. A outstanding ex mple is the report by Kincaid Smith nd col leagues that 5 out of 7 of their patient survived with stable renal f nction for over yea (71 per ent) nd 11 of 14 ho received graft more tha 6 months ago (78 per cent). All their deaths oc curred ithin the first 6 eek after grafting Results

of this order reduce the alleged superiorit of the related donor kidney over the cada eric kidney almost to anishing point It ma ll be that results as good as there can be obtained only in center here ll energies are devoted to cada eric transplantation

I the liv ng donor there is time for tissue ty ping to be carried out, hereas t has seldom or never been possible to pply these techniques in the cadaveric situation due to the time limitation There are encouraging reports, however hat the lif of the kidney outside the bod ma be prolonged considerably Ackerman and associates[6] report immediate good f nction in dog autotransplants after 24 to 48 hours storage ith h pothermic perfusion in hyperbaric ox gen Belzer nd associates[7] has reported normal function in dogs thin 3 eeks hen the kidneys ere preserved for 72 hours by hypothermic perfusion ith the use of membrane oxygenator E tension of the extracorporeal lif of the kidney to 24 hour ould be adequate for tissue yping as ll tor preparation of the recipient nd mobilization of the transplant team

F en thout the mor elabor t methods of kidney preserv ion, it is still possible to achiev sort of partial tissue ty ping by prelim nary t ping of the recipients If hey are found to lack most or ll of the an igens onsidered importa t in transplantation, such patient ould pr babl be d fficult t match and ould probabl be better managed by inter mi tent dialysis P ients ell furnished th antigens ould on the contrary ppear to be in more f orable position nd ould be given preference in he transplantation progr m

Theoret all siblings hould ha better chance f gr ng long term surv ng grafts han parent but he recent anal es f the Registry result by Barnes ha not produced tatistical evidence of this It astonishing that so many pa ients all over the orld surv th good kidney function after re eiving ada eric kidney hen he only form of ma hing used as major blood group compatibilit

I the thor ow series of pa ients referred for ad eric transplanta ion, 6 of 7 survived one for 10 months, he emainder f om 17 to 33 month Another patien ho recen h eceived adaveric t splant rema ns ell lthough the graf failed for echnical reason and as removed Since fa lure f first graft does not ppear prejudice he fat of l er graft ther seems no re son to suppose that his patien ma not ha bet er fortune nex time I his small bu encouraging group of patients the major bl od groups only er considered The limited tissue ping described bov has been arried out on he pa ien urrently aiting ranspla ts

Good prepar ion f patient th period f dial sis sufficien restore nearly normal nutr onal nd bioch m l ta probabl ontributes gr h he consider ble improvemen the transplanta ion stat t Increased experience has also helped to educ ss kne l surgical failures especiall ith regard to he ur er lthough some such f lures continue to occur Incre sed experience h mm nosuppress ther py h ho contributed nd further improvement an be hoped for by he se of antil mphocy and antithym sera. The tissue ping methods ma also help here

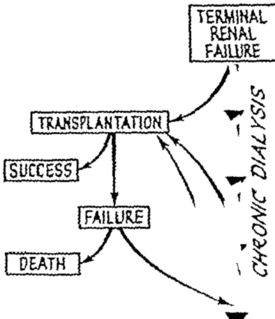


Fig. 1

by reducing the strength of the incompatibilit barrier hich has t be overcome and perm tting the use of lesser amou or less toxic methods of immunosuppression Nevertheless sur has already been show that suc essf l result f approach ng 80 per en be obtained in he appar ently random matching f ada eric kidney best the tissue ping techniques annot be expected make more tha 20 per en impro ement

I is ery lear tha suc essful kidney transplantation progr m depend association h ell organized dialysis serv e hich can make patients h and keep hem ht I an opportunit for transplanta ion or T nsplantation should not be carried ou almost as an emergency an ht patien Indeed he ery ailabil f he kidney in the liv donor uation ma ha led to failures in the past hen his as not learly recog nized nd he kidney as transplan ed quickl

ood the necess for maintenanc dial When cada eric kidney is to be used is nearl l obligatory to art for period before suitable kidney is found, this period being performed used to dialyses the pa ien nd impro his fitness

The relationship bet een h on dialysis and transpla tat on is illust ted in Fig I All patients ho are erminal enal failure are h and require dial sis to make hem fit for he oper tion One they become fit anspla ta n an be arried out t any time thereafter ha is onvenient Although it is likel ha some r nsplan ll fail, failures are learly becoming fewer nd f lures if recog ized earl nd he kidney removed, should not result in he death of the patient. The dialysis program should be able ac ept these patien al and keep them fi ti nd obtained.

The ...rsed ... es achieved ... ith ... adax ... ic t nspla... m ... nak ... t ... neth ... al t ... onsider ... m ng kidnes f om ... nung h ... donor ... pes ... ffs from ... sma ... h ... pei his ... pers l of lif. There ma t ll ... soon ll be ... ie ... m t ... oces n wh h ... kidnes from ... pu ... sold ... mall be used especially if he pari t ... ld ... nough ... ha ... sp ... nsibility for ... ou ... ic t ... I ... It is ... mplet h ... j t hed to ... kidne ... om ... nrelated h ... donor ... h h ... les ... gr ... tk ... lihi ... d of suc es ... than ... ad kidnes

I am g t f l t M ... Joseph A Kenned ... M Ch F R C S for perm ... to ... quot the detail of his patie t

M ... C M Cou... M I ... Ph D ... M R C P (Ed ...)
Con ultant Medic l ... olog st
Department of N ph olog
Bell ... l Cit Hospital
I ... sb ... n Rd
Department ... f Medicin
Quee ... l ... ser ... it
Belfast ... N Ireland

REFERENCES

1 ... Ack ... rma ... J K ... H pkinson ... W ... I and Ken ... J R ... Nee ... essf l 24-48 hour ... nine kidnes preserv tion Eur ... pe ... Dialy is & T ... nsplant Association 1967
2 Belzer F O ... Ashby B S ... nd Dunph ... J E 24-hour and 72 hour preserv tion of canine kidney ... Lancet ... :536, 1967
3 Frankson C ... C ll te L Lundgren, C ... Mag ... sson, C ... and W hle B ... Kidney tra splantation ... 1964-66, ... t Serafimerlasarettet and St. Erik ... H spit l, St ckholm ... Scand na ... J Urol Neph ol 1:81 ... 1967
4 Kincaid Sm th ... I ... Marshall V ... C ... M thew T H ... Er m n, J ... Brown, R B ... J hnson, N ... I ... ell R R H ... M Leish, D C ... I ... rdes ... K F ... Mler ... k, F ... A ... nd F ... ing M R ... Cada eric renal t ansplant tion, Lancet 2:59 ... 1967
5 Le k ... C D ... The changing mores of biomedical rese rch ... Ann Int Med (Suppl 7) 6 ... :36, 1967
6 Liljeq ist I ... Gener l health ... nd renal f nct on in kidney t ansplant tion donor ... 8-30 month aft ... nephrect my ... Scandinav ... J Urol Nephrol. 1:156, 1967
7 Murra ... J E ... Barnes B A ... and Atk nson, J Fifth report ... of the human kidney t ... nsplant registry ... Transpla tation 5 752, 1967
8 Starzl, T E ... The ... hanging mores of biomedical rese rch ... A ... I t ... Med ... (Suppl ... 6 :36, 1967

Individual glomerular filtration rates in renovascular hypertension

More tha ... 30 ... ar h ... passed since Goldblatt ... nd ... ssociates fi st reported the exper mental production of persist ... t h pertension by producing renal ischemia ... Th ... ... tion ... followed short thereafter by B tler ... report of the first suc essf ll tre ted ... se of renal h pert nsion by nephrectomy. Wh le en husia m ... in full ... gr ... t It soon bec me pparent that fewer tha ... 25 per cent of surgically trea ed patient ... ere ac ually ... ured of hypertension ... hich h ... presumabl of enal orig ... Better meth od ... nd criteria for the selection of surgical cand dates ... ere needed and differential renal f nction t dies emerged as one of many method ... to ... help the ... li ician select hypertensi ... patient ... ith uni lateral renovascular disease ... hom ... cure by surgical intervention might be expected

The usefulness of differential renal function studies cannot be denied. The ... arious methodology for their performance and criteria for their interpretation which ha ... been introduced since the early work of Howard and associates[1] ... nd Connor ... nd co-workers[2] ... ttests to the fact that no one method or criterion ha ... been uniformly satisfactory in indicating which patient ... re ideal candidates for correctly surgery. Perhaps disappoi tment ... differential renal function studies arises from the fact that as originally proposed[1-4] they are all based upon ... inherent fallacy ... that is, they are comparati... in nature ... nd use as the ... t ndard for comparison ... nous pa ... meter ... of funct on of the contr lateral kidney (that opposit ... the k lney ... ith suspected impaired arterial ... upply) ... h h i ... arbitrarily designated ... being ... norm l. Thus i ... the presence of ... nsuspected bilateral renal disease ... ether ... it is parenchymal or ... ... cular or ... combination of the ... t ... the standard for ... omparison is often in error and unrecognized as such by the clinician. Before differential renal function studies ca ... be mea ingful ... nd be relied upon as an aid for the selection of surgical candidates ... ho may reasonably be expected to be cured of hypertension, adequat ... proof tha ... the so-called ... normal kidney ... is i ... fact normal must first be established

W ... recentl ... studied 101 hypertensi ... patients by differential renal f nction studies. 23 of whom had unilateral mal ... renal artery ... tenosis and ... ere oper ... ted upon. Nine of the 23 patients ... ere not surgically cured. All of the 14 patients who ... ere cured by surgic l procedures (re ... scularization or ne phrectomy) had ... positiv ... differential renal function stud ... by ... t least two of three cri eria. ... Somewhat discouraging ... as the fact that the majority of those patients ... hose blood pressure did not respond to surgical treatment ... ho had positi ... differential renal f nction studies. I ... 12 of the cured patients and in 7 of those ... ho ... ere not cured, ... estimat ... of the glomerular filtration rate (GFR) of each kidney ... made by calculating the endogenous

creatinine clearance from urine nd blood specimens obtained t the time of bilateral ureteral catheterization It was pparent that, i those patients in whom the CFR in the contr lateral kidney as normal or not reduced by more than 25 per cent of normal, cure could reasonably be expected. By demonstrating that the "normal" kidney was indeed f nctionally normal, the predictiv accuracy of differential renal f nction studies was substantially improved.

Vertes and associates[10] have stressed the desir ability of establish ng that the "normal" kidney is fact normal, using as their criterion normal tissue architecture observed biopsy specimens obtained from the co tralateral kidney However there is insufficient evidence to support the thesis that function precisely parallels architecture or that the pathological changes hich are observed are totally irreversible Indeed t has been reported that surgical cures ha been obtained in patients with unilateral main renal artery tenosis in hom reduced renal function was present the contralateral kidney This as true one of ou ow patients[13] However in fiv of our patients, hom contra lateral renal f nction as significa tly impaired, cure as not obtained regardless of whether the differential renal function tudy was positiv by other criterion for nilateral renal artery stenosis.

Since differential renal f nction studies compare one kidney function ith that of the other they are less accurate in the presence of bilateral disease hether the disease is small or large essel in nature I ou experience the accuracy of differential renal f nction tudies is greatly enhanced hen n estimation of the glomerular filtration rat or renal plasma flow of each kidney is made t the time of bilateral reteral catheterization. Stamey ha pointed out the alue of measuring the glomerular filtration rates or renal plasma flow of each kidney W prefer the former because of its relativ simplicity and because feel it more accurately reflects the trarenal functional capacity

Richard A. Schacht M.D
Assistant Chief of Internal Medicine
Research Associate
United States Public Health Service Hospital
New Orlea La
J me Conwa Ph.D M.D
Associate Professor of Internal Medicine
University of Michigan Medical Center
Ann Arbor Mich.

REFERENCES

1. Goldblatt, H Lynch J Hanzal R F nd Summerville W W Studies on experimental hypertension. I The production of persistent elev tion of systolic blood pressure by means of renal ischemia, J Exper Med. 59:347 1934
2. B tler A M Chronic py lonephritis and arterial hypertension, J Clin Invest. 16:889 1937
3. Smith H W Hypertension nd urologic disease, Am. J Med 4 724 1948
4. Howard, J E., Berthrong M Gould, D M nd Yendt, E. R. Hypertension result ng from unilateral renal ascular disease and ts relief by nephrectomy Bull Johns Hopki Hosp 94:51 1954.
5. Connor T B Berthrong, M Thomas, W C. J and Howard, J E. Hypertension due t unilateral renal disease with report on functional test helpf l in diagnosis, B ll Johns Hopkins Hosp 100:241 1957
6. Rapoport, A. Modification of the Howard Test for the detection of renal artery obstruc tion, New England J Med 263:1159 1960.
7. Stamey T A. The diagnosis of curable i lateral renal hypertension by ureteral catheterization, Postgrad. Med 29:496 1961
8. Birchall, R Batson, H M J nd Bra na W Contribution of differential renal studies t the diagnosis of renal arterial h pertension, Am J Med. 32 164, 1962.
9. Schacht, R. A Conway J and Stewart B H Split renal function studies in hyper tension, Arch. I t Med 119:588, 1967
10. Vertes, V Grauel, J A and Goldblatt H. Renal arteriography separate renal f nction tudies, and renal biopsy in h man h pertension selection of patients for surgical treat ment, New England J Med 270:656, 1964
11. Vertes, V Gen th, S Leb, D F nd Gal n, J B Unilateral renal plasma flow in the assessment of correctable renovascular h pertension, New England J Med 273:835 1965
12. Strickler W L Surgical trea ment of renovascular h pertension, New England J Med 274:52, 1966
13. Schacht, R A Z eifler A J nd Con J Renal artery stenosis New England J Med 271:55 1964
14. Stamey T A I Gross, F ed or A tih per tensive therapy Berl 1966, Springer Verlag

Catecholamines and myocardial damage in scorpion sting

Various species of scorpions ha arious kinds of poison that differ from one nother chemical structure nd ph siological effects. The effect of the st ng depends pon he age of the sc rpion the season, and the size of the ictim

Myocardial damage nd heart fail re are not frequent complication in scorpion sting nd ha not been thoroughly investig ted. Although the manifestations of scorpion are ttributed t neurotoxic effect, the basic mec ha ism of cardiac damage and consequ heart failure remains obscure. Furthermore pathological observ tions of the cardiovascular system in fatal scorpion t ng are scarce.

Electrocardiographic abnormalities ha been reported in some patients nd ttributed to toxic

Table I In in rea of catecholamine metabolites excretion

	1st day		2nd day	
	Total free catecholamines (γ/24 hr)	Vanilmandelic acid (γ/mg)	Total free catecholamines	Vanilmandelic acid (γ/mg)
V. S.	32	16		6
V. M. t	100	17		2

ormal alues or ... rent (aged 2 ... are ... Vanilmandelic acid ... per milligram of creatinine in urine ... total free catecholamines ... per kilogram per 24 hours
Normal values ... patients aged 2 ... vanilmandelic acid 3 ... 3 ... per milligram of creatinine in urine ... free catecholamines 20 ... 60 ... per 24 hours ... rent

... of scorpion venom on the heart. Although pathological ... myocardial damage ... lable.

... reported ... patient with scorpion ... accompanied by heart failure ... those ... cular manifestations ... the venom ... attributed to increased ... pressor amines the result of direct effect of scorpion venom on the adrenals ... the sympathetic nervous system. The electrocardiographic changes were consistent with ... myocardial infarction-like pattern ... be the result of catecholamine-induced hypoxia through direct ... interference ... accompanied by elevated serum transaminases. This was substantiated by the lack of morphologic changes of the myocardium ... fatal cases despite heart failure or pulmonary edema.

In 1954 ... review of the clinical manifestations of scorpion sting, Barsoum and associates suggested that the majority of the ... of the venom are due to the presence of large amounts of circulating epinephrine. They reported increased plasma epinephrine count ... patients who were examined 12 hours after the sting, the plasma epinephrine ... the normal level. Other authors expressed similar ... on the basis of experimental data but biochemical confirmation of increased circulating catecholamines ... scorpion sting was not available.

Two patients who, after ... sting by the yellow scorpion, *Buthus quinquestriatus* (commonly found in southern Israel) had heart failure and electrocardiographic changes similar to those reported in ... previous communication, were recently observed. Excretion of catecholamine metabolites was investigated in both patients during the first 48 hours after the sting. Except for mild sedation, medication was initially omitted. As clearly seen in Table I, prominent increase of catecholamine metabolite excretion was present during the first 24 hours in both patients, substantiating our assumption of an increase in circulating pressor amines. These results establish that the cardiovascular manifestations of scorpion sting are the clinical counterpart of the venom effect on the adrenals and sympathetic nervous system. Furthermore, ... effect of scorpion venom and epinephrine has recently been reported. All these ... point out that the ... of both scorpion sting ... individual ... and the neurotoxic effect of the venom ... probably less important.

Moshe Gueron, M.D.
Shimon Weizman, M.D.
Cardiac Laboratory, The Negev Central Hospital
Beersheba, Israel

REFERENCES

1. Shulov, A.: On some Israel scorpions, Dapim Refuim 21:657, 1962.
2. Sterman, N.: Scorpion sting poisoning in the Negev, Dapim Refuim 21:661, 1962.
3. Stahnke, H. L.: The Arizona scorpion problem, Arizona Med. 7:23, 1950.
4. Gueron, M., Stern, J., and Cohen, W.: Severe myocardial damage and heart failure in scorpion sting, Am. J. Cardiol. 19:719, 1967.
5. Lim ... King, T.: Myocarditis from scorpion sting, Brit. M. J. 1:374, 1963.
6. B... and ... A., and R... der, A.: The Heglin syndrome ... myocarditis due to scorpion sting, Harefuah 73:14, 1967.
7. Raab, W.: Key position of catecholamines in functional and degenerative cardiovascular pathology, Am. J. Cardiol. 5:571, 1960.
8. Gueron, M.: The pathology of the myocardium in fatal scorpion sting. Unpublished observations.
9. Barsoum, G. S., Nabawy, M., and Salama, S.: Scorpion poisoning—Its signs, symptoms and treatment, J. Egyptian M. A. 3:857, 1954.
10. Patterson, R. A.: Physiologic action of scorpion venom, Am. J. Trop. Med. 9:410, 1960.
11. Ruh... m, H.: Scorpion toxin and ... tonomic drugs, J. Trop. Med. 56:150, 1953.
12. Stahnke, H. L.: Stress and toxicity of venom, Science 150:1456, 1965.
13. Cutting, W. A. M.: Letter to editor, Brit. M. J. 1:374, 1963.

14. Poon King T Letter t editor Brit. M J 1:1016 1963.
15 Herman, G A. The determination of urinary 3-Methoxy 4-Hydroxymandelic (Vanilmandelic) acid by means of electrophoresis with cellulose acetate membrane, Am. J Clin. Path 41:373 1964
16. Donough, O and Ibbot, F A Estimation of pressor amines metabolites in urine Laboratory manual of pediatric micro and ultramicro biochemical technics, Hoeber Medical Books, 1962, Harper & Row p. 169
17 Von Euler U S. and Floding I Diagnosis of pheochromocytoma by fluorometric estimation of adrenalin and noradrenalin in urine, Scandinav J Clin. & Lab. I vest. 8:288, 1956.

Extracellular volume in patients with chronic renal disease treated for hypertension by sodium restriction

It has been demonstrated in majority of patients undergoing mai tenance hemodialysis that hyper tension can be controlled successfully by reducing body weight using ultrafiltration Patients with chronic renal failure who are being managed conservatively often require adequat control of total body sodium for the treatment of their hypertension, which tends to be resistant to drug treatment in the presence of sodium excess It was of particular interest to determine hether extracellular olume (ECV) and exchangeable sodium (Na_e) had been lowered below normal in patients ith chronic uremia in whom reasonably good control of blood pressure had been achieved by restriction and/or removal of sodium ECV and Na_e were measured w th radioacti bromine-82 and sodium-24 respectively I ten health controls both ECV and Na_e ere very closely related to lean body mass determined by method hich incorporates the measurements of body weight, height, and skin-fold thickness Of eight patients with chronic renal insufficiency seven had decrease in blood pressure concomitant with the use of sodium restriction as the principal form of treatment Measurements of EVC and Na_e ere with but one exception ithin or abov the normal range. Four patients on long term hemodialyses had an elevated ECV and Na_e before routine dialyses. Dialysis decreased the two parameters to normal but not below in all as well as in tw more patients investigated only after dialysis With one exception blood pressure, hich had been moderately elevated predialysis, was reduced to normal levels concomitantly Two of these patients had been severely hypertensive t the time when regular dialysis treatment was started. When interpreting data of body spaces, one should question if measurements related to body weight or even lean body mass as reference point in patients with chronic disease can be validly compared to values obtained in healthy controls. Malnourishment and asting of the body cellular mass can result in relati increase of the extra cellular compartment. However in the study mentioned above patients ere selected only if they were physically active and had maintained stable body weight. Therefore it seems valid to state that in the tw groups of patients satisfactory blood pressure control wa achieved when ECV and Na_e were reduced to normal levels. It should be pointed out that in man patients time lag exists between reduction of these parameters and adequate control of blood pressure, which may require several eeks. These experiments demonstrate the importance of w ter and electrolyte balance for the managemen of hypertension in chronic renal disease. However it is quite evident that other importa t factors must be operative in the pathogenesis of this form of hypertension It has been shown that in small minority of patients on maintenance dialysis efficient removal of fluid over prolonged period of time will not result in correction of hypertension I these patients, bilateral nephrectomy will usually normalize blood pressure, which then will become dependent only on the state of hydration and sodium balance These findings support the hypothesis of renal pressor system contributing to the hypertension. The nature of this pressor system is still matter of conjecture Increased concentrations of ren (in peripheral blood as well as in kidney tissue) have been found in some patients but not in all I occasional patients, h pertension persisted even after bilateral nephrectomy but was corrected by successful renal transpla tation. It is not entirely clear whether adequate removal of fluid and sodium had taken place in these cases before transplantation. Nevertheless, they may represent an argument in favor of renoprival componen of the hypertension

Alfred Bl mberg M.D
Medizinische Poliklinik
University of Bern
Switzerland

REFERENCES

1 Scribner B. H Fergus, E. B., Boen, S T and Thomas, E. D Some therapeutic approaches to chronic renal insufficiency Ann. Rev Med 16:285 1965.
2. Scribner B H. I Black, D A. K., editor Renal disease, Oxford, 1967 (In press)
3. Edwards, K. O C and Whyte, H. M Creatinine excretion and body composition, Clin. Sc. 18:361 1959
4 Blumberg, A Nelp, W R., Hegstrom, R. M and Scribner B H. Extra cellular volume I patients ith chronic renal disease treated

for hypertension by sodium restriction, Lancet 2:60, 1967.

5. Herschel, A., Mickelsen, O., Taylor, H. L., and Keys, A.: Plasma volume and thiocyanate space in famine edema and recovery, Am. J. Physiol. 149:1, 1947.
6. Moore, F. D., Olesen, K. H., McMurrey, J. D., Parker, H. V., Ball, M. R., and Boyden, C. M.: The body cell mass and its supporting environment, London, 1963, p. 23.
   Funck-Brentano, J. L., Chaumont, P., Perrin, D., Zingraff, J., and Vantelon, J.: Traitement de l'urémie chronique par les hémodialyses répétées, Actualités Néphrol. Hôp. Necker 1965, p. 45.
8. Hume, D. M., Lee, H. M., Williams, G. M., White, H. J. O., Ferré, J., Wolf, J. S., Prout, G. R., Jr., Slapak, M., O'Brien, J., Kilpatrick, S. J., Kauffman, H. M., Jr., and Cleveland, R. J.: Comparative results of cadaver and related donor renal homografts in man, and immunologic implications of the outcome of second and paired transplants, Ann. Surg. 164:352, 1966.
9. Blumberg, A.: Unpublished observation.
10. Merrill, J. P., and Schupak, E.: Mechanisms of hypertension in renoprival man, Canad. M. A. J. 90:328, 1964.
11. Shibagaki, M., Wolff, W. J., Haas, E., and Goldblatt, H.: Concentration of renin in kidneys of patients with renal hypertension, Lancet 1:1217, 1965.
12. Blaufox, M. D., Birbari, A. E., Hickler, R. B., and Merrill, J. P.: Peripheral plasma renin activity in renal-homotransplant recipients, New England J. Med. 275:1165, 1966.
13. Kolff, W. J., Nakamoto, S., Poutasse, E. F., Straffon, R. A., and Figueroa, J. E.: Effect of bilateral nephrectomy and kidney transplantation on hypertension in man, Circulation (Suppl. 2) 30:23, 1964.

Letter to the Editor

Combined propranolol and quinidine treatment in cardiac arrhythmias

To the Editor

We have read with great interest the first communication and the latest extensive work by Stern,[1,2] concerning the combined propranolol and quinidine treatment in chronic atrial fibrillation. We have been carrying on a similar clinical treatment for several months with altogether less favorable results as regards conversion to sinus rhythm but in full agreement concerning the maintenance of sinus rhythm when achieved.

So far we have treated exactly 13 patients, all of them suffering from long standing atrial fibrillation (over 6 months). We usually administered 60 mg. of propranolol in three or four divided oral doses for 3 days, and followed up this treatment during administration of quinidine. Quinidine was administered in five oral doses of 0.1 gram during the first day, in five oral doses of 0.2 gram during the second, and six oral doses of 0.2 gram during the third and fourth days. The interval between doses was 2 hours. A moderate digitalis and anticoagulant medication was associated.

In one patient suffering from mitroaortic valvular disease conversion to sinus rhythm was achieved in the first day after only 0.6 gram of quinidine.

In 7 out of 10 patients, sinus rhythm was achieved after 3 to 4 days of treatment (similar results, however, were obtained with quinidine alone in approximately 200 cases). Finally two trials were successful, while previous treatment with quinidine alone in the same patients had given no results.

After the conversion, all the patients were maintained on the combined treatment of the two drugs, in some cases propranolol being substituted by butidrine, another β-blocking agent closely related to propranolol from a chemical point of view. The usual doses of these compounds were 0.2 gram of quinidine every 8 hours and 20 mg. of propranolol or 50 mg. of butidrine every 12 hours.

Sinus rhythm has been maintained in 8 out of 9 patients for a period varying between 3 and 14 months. In one case atrial fibrillation relapsed because the treatment was discontinued.

We must add four more cases of frequently recurrent paroxysmal atrial fibrillation: crises completely disappeared in three patients; in one they were mitigated after treatment.

We want to point out the importance of this maintenance therapy in patients with tendency to atrial fibrillation. In fact, all the fantastic progress achieved in the field of conversion to sinus rhythm (especially with electrical defibrillation) appears to be of negligible practical use considering the fatal tendency of this arrhythmia to relapse except when the cause of the arrhythmia is known and eliminable.

During this combined therapy we did not observe any remarkable side effect and this is in accordance with a parallel pharmacological study we have carried on on the isolated rabbit heart.

On this preparation propranolol, as already observed,[3] causes an evident negative inotropic effect with the dose of 0.25 μg per milliliter of the nutrient fluid, per cent reduction in comparison with basal levels arbitrarily taken as 100 was -50.0 ± 8.8 per cent. The same may be said in regard to quinidine, which in our experiments provoked a per cent reduction of the contractile force of -40.2 ± 8.1 per cent at the dose of 1 μg per milliliter.

The association of the two drugs surprisingly enough, far from enhancing the single negative effects, actually reduced them. The per cent reduction after the association of 1 μg per milliliter quinidine + 0.25 μg per milliliter of propranolol was in fact lower than the single reductions observed after each drug (-34.7 ± 4.2 per cent).

It is deemed of interest that this phenomenon was observed in preliminary experiments[4] even combining quinidine with butidrine as already mentioned in the clinical trials.

This work was partly supported by a grant from the Consiglio Nazionale delle Ricerche, Rome.

Odoardo Visioli
Institute of Medical Clinic and Medical Therapy
Giulio Bertaccini
Institute of Pharmacology
University of Parma
Parma, Italy

REFERENCES

1. Stern, S.: Synergistic action of propranolol with quinidine, Am. Heart J. 72:569, 1966.
2. Stern, S.: Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment, Am. Heart J. 74:170, 1967.
3. Levy, J. V., and Richard, V.: Inotropic and chronotropic effects of a series of β-adrenergic blocking drugs: some structure-activity relationships, Proc. Soc. Exper. Biol. & Med. 122:373, 1966.
4. Levy, J. V.: Inotropic and chronotropic effects of six β-adrenergic blocking drugs on the isolated rabbit heart, Internat. Congr. Pharmacol., São Paulo, 1966.
5. Bertaccini, G., Impicciatore, M., Malagnino, G., and Visioli, O.: Inotropic and chronotropic effects of two stereoisomers of butidrine, a new adrenergic β-blocking agent, on isolated rabbit heart, and rat auricles, Il Farmaco, 1968, in press.

Book reviews

HYPT 11 I I N SPUL R DIS ST DIAGNOSIS AND TR A MEN B Mars M ser M D F.A C.I nd Arthur C Goldma M D Philadelphia and Toront 1967 J B Lippincott Company 343 pages Price $12 00

Drs Moyer and Goldman ha written relatively concise book on common nd important disease of ma They discuss basic problems, ie. examination of the pa ient renovascular hypertension renal h pertension endocrinopathies associated w h h pertension essential hypertension nd tre tment They discuss drugs primarily concerned w th the management of hyperten ion Their presentations, as would be xpected represent their ow concepts. Essen l h pertension is di ided into fou groups the than benign and malignant They seem de-empha ize the psy hogenic and neurogenic fac or h pertension Nevertheless, this is ndensat on of n extensiv subject and problem about which much ha been written Th thors summarize the action nd nature of the drugs sed as ll the dosage and method of sing them f rly w ll. There is good ndex and good illustrations. They seem t overemphasize renov s lar hypertension out of proportion t it importance i the entire cli ical field of high blood pressure Nevertheless, this is useful book with concise nd ready source of information on hypertension

ULTRASTRUCTURE OF THE KIDNEY ol 2. Ed ted by Albert J Dalton and Francoise Haguenau New York, London, 1967 Academic Press, Inc 240 pages. Price $14.00

The recent developments better nderstanding of the relations of tructure t function of the kidneys ha e interested physicians i linical practice as well as the investigators themselves The electron microscope ha opened a new field i medicine and the instrument has been pplied very well t the normal and diseased kidneys. Although study of the ultrastructure of the kidneys is *in its infancy much has lready been* done. This monograph through the efforts of ten contributors, summarizes the present stat of knowledge ery well. The many electron micrographs are very good. The chapters include discussions of the fine tructure of renal tubules in the cortex and medulla, structure and function of the glomerular mesangium some morphological considerations of transport in the glomerulus the juxtaglomerular apparatus, and ultrastructural pathology of the glomerulus. The presentations are all ery good though necessarily brief The reader will find this an extremely interesting book and profitable one to study

CLINICAL PLETHYSMOGRAPHY OF THE FOREFOOT IN ARTERIOSCLEROSIS OBLITERANS. By Ole Munc Copenhagen 1967 Ejnar M nksgaard Forlag, 191 pages.

This is rather brief discussion of plethysmography in man a applied t the forefoot of man with arteriosclerotic disease The presentation is not a critical one No attempt was made t evaluat the problems as difficulties involved in plethysmography Dr M nc present the plethysmography as it is con entionally employed and the records I terpreted H does emphasize the importance of the clinical tudy in which pleth smography is supporting procedure This is short presentation nd, therefore, would be expected to be incomplete The method as commonly employed ha considerable quantit th limitations. However it is an extremely usef l procedure when employed with considerable care and with ttention to detail. This is usef l book on an importa t subject which is much neglected in medicine that is peripheral vascul r disease

BALLISTOCARDIOGRAPHY IN CARDIOVASCULAR RESEARCH By Isaac Starr nd Abraham Noordergraaf Philadelphia/Montreal, 1967 J P Lippincott Company 438 pages. Price $20.00

This is n authorit tive book on ballistocardiography (BCG). Doctor Starr originated, developed and taught BCG over ma y years H rot this book with Doctor Noordergraaf who has been responsible for the most important instrumental and physical contributions in the field. The t uthors have produced an excellent book. The presentations are divided into essentially three parts, (1) the instrumental and theoretic (2) physiologic; and (3) clinical The presentations are lear highly and clearly illustrated, and supported by a complet bibliography This book is welcomed and recommended t beginners as well as trained h icians as an excellent discussion of the BCG.

BURNS, SHOCK AND PLASMA VOLUME REGULATION By Carl A. Moyer M D and Harvey R. Butcher J M D St Louis, 1967 The C. V Mosby Company 428 pages. Price $18.50

This monograph summarizes the studies and opinions of the authors concerning burns, shock, and plasma olume regulation. These complex problems have captured the *i terests of the senior* thor for many years. The book is well orga nized, highly illustrated, and clearly written so that the reader will find it easy to nderstand the authors points of iew Each chapter is supported by a bibliography The appendix sum-

marizes experimental data on their dogs and patients. They as everyone, ha difficulty not only in defining shock but also in indicating the fundamental physiological disturbance responsible for the state. Nevertheless, the book contains formulas for calculating plasma volume, electrolyte and water needs in shock, and severe burn as well as methods for replacing water and electrolytes Those engaged in study of these subjects will find the book of interest. It provides good summary of the clinical and experimental experiences of the authors.

CARDIOVASCULAR PHYSIOLOGY By Robert M. Berne, M D and Matthew N Levy M D St. Louis, 1967 The C V Mosby Company 254 pages. Price $10 75

This book summarizes ery well some selected principles of physiology of the heart and circulation. Students of physiology and medicine will find this ery useful as start in their studies of the circulation. The illustrations are conventional ones, accurate and ery clear The bibliography is brief nd good though limited mai ly to the recent literature. This is afortunate It is not extensive enough to include some of the best publications of earlier years The principles presented are for the normal cardiovascular systems and do not include tudies of disease states which have made it possible to understand even better the normal stat This monograph does not replace the sections on the heart and circulation contained in the standard textbook of physiology the *H ndbook of Physiology* or the classic review and monographs but it should be very usef l t those beginning to study the circulation. It is to those readers that this book is recommended by the authors

A CURRENT TECHNIQUE OF AORTOILIAC AND FEMOROPOPLITEAL ENDARTERECTOMY FOR OBLITERATIVE ATHEROSCLEROSIS. By Jack A. Cannon, M D Springfield, Ill 1965 Charles C Thomas Publisher 54 pages. Price $4.75.

Dr Cannon has been one of the leaders in the use of endarterectomy for obliterativ arteriosclerosis of the lower extremities. I this small olume he rigorously restricts discussion to the technical aspects of operation although some consideration is given to patient selection Descriptions are thorough. Illustrations are good. The volume achieves its purpose well. Reference is made in several places t the uthor technique of transbrachial aortography It would ha improved the ork considerably if this technique were also described in detail. A reference in the bibliography will lead an interested reader t this technique if he makes a trip to the nearest medical library

CLINICAL HEMATOLOGY By Maxwell M. Wintrobe 6th edition, Philadelphia, 1967 Lea & Febiger Publishers, 1,287 pages. Pri. $22.50.

EKG-FIBEL. By Rolf Heinecker Stuttgart, Germany 1967 Georg Thieme Verlag 316 pages.

EPIDEMIOLOGIA DE ENFERMEDADES CRONICAS Y ACCIDENTES EN CHILE, VOLS. I AND II By Ernesto Medina L., Santiago, 1966, Universidad de Chile. 358 pages.

INSURANCE FOR THE DOCTOR. By Harvey Sarner and Herbert C. Lassiter Philadelphia, 1967 W B. Saunders Company 193 pages. Price $9.00

INTESTINAL ABSORPTION British Medical Bulletin, Vol. 23 No. 3, September 1967 Edited by D H. Smyth, London, 1967 Medical Department British Council, 296 pages. Price $5.00.

KLOCK & TABLES OF RANDOM NUMBERS. By John M Klock and James W Klock, Detroit 1967 Central Publishing 30 pages. Price $2 00.

POSSIBILITA DI CURA DELLA ARTERIOSCLEROSIS CON LA GONADOTROPINA CORIONICA. By Vittorio Scaffidi, Italy 1967 Edizioni Minerva Medica, pages 2,343 to 2,369

A GUIDE FOR HEALTH TECHNOLOGY PROGRAM PLANNING. National Health Council, New York, N Y., 1967 52 pages Price $1.00 per copy

HANDBOOK OF CONGENITAL MALFORMATIONS. By Alan Rubin, Philadelphia, 1967 W B. Saunders Company 398 pages Price $14.00

MODERN TREATMENT Vol. 4 N 4, July 1967 (1) Advances the Treatment of Poisoning, by J v M Arena. (2) Treatment of Mental Retardation Part I by Charles M Poser New York, 1967 Hoeber Medical Division, Harper & Row Publishers, Inc., 1,600 pages per year Price $16.00 per year

MODERN TREATMENT Vol 4 No. 5 September 1967 (1) Treatment of Meningitis by William S Fields. (2) Treatment of Mental Retardation Part II by Charles M Poser New York, 1967 Hoeber Medical Division, Harper & Row Publishers, Inc., 1,600 pages per year Price $16 00.

PROJECT HEAD START Office of Economic Opportunity Washington, D C., 1967 73 pages.

ALLGEMEINE UND SPEZIELLE CHIRURGISCHE OPERATIONSLEHRE ZWEITE AUFLAGE VI/1 DIE EINGRIFFE AN DER BRUST UND IN DER BRUSTHOHLE By Alfred Brunner with H. G. Borst, F Deucher H. Hamelmann, G. Hossli, W Klinner W Overbeck, H J Peiper G. Tondury and A. Widmer New York 1967 Springer Verlag, 969 pages.

INTERPRETIVE ENZYMOLOGY By John G Batsakis and Russell O Briere Springfield, Ill., 1967 Charles C Thomas Publisher 291 pages. Price $12 50.

KREISLAUFFUNKTION IN WILLIAM HARVEYS SCHRIFTEN. By Walter L. von Brunn, New York 1967 Springer Verlag 161 pages. Price $8.00.

PORTAL HYPERTENSION By Cornelius E. Sedgwick and Joh K. Poulantzas Boston, 1967 Little Brow & Co 257 pages. Price $13.50

PSYCHIATRY IN AEROSPACE MEDICINE Vol. 4, No. 1 by Carlos J G. Perry International Psychiatry Clinics Winter 1967 Boston, 1967 Little, Brow & Co., 238 pages. Price $8.50.

Announcement

The Third International Symposium on Drugs Affecting Lipid Metabolism will be held in Milan, Italy, from Sept. 9 to 11, 1968. The Joint Scientific Secretaries are Dr. W. L. Holmes, The Lankenau Hospital, Philadelphia, Pa. 19151, and Prof. R. Paoletti, Institute of Pharmacology of the University of Milan. The sessions will be divided as follows: Drugs affecting (1) FFA mobilization, (2) Triglycerides, (3) Cholesterol and bile acid metabolism, (4) Serum lipoproteins, (5) Tissue lipids and obesity, (6) General. For further information contact: Miss H. J. Praus, Institute of Pharmacology, University of Milan, Via A. del Sarto 21, 20129 Milan, Italy.

The Thirteenth Ballistocardiograph Research Society Meeting will be held at Haddon Hall, Atlantic City, N. J., May 5, 1968. For information contact: N. Ty Smith, M.D., Department of Anesthesia, Stanford Medical Center, Palo Alto, Calif. 94304.

The foreign visitors will be: (1) Dr. A. G. Morrow, Chief, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md., U.S.A.; (2) Professor G. E. Burch, Professor of Medicine, Tulane University, New Orleans, U.S.A., Editor of The American Heart Journal; (3) Dr. A. J. Beuren, Professor of Cardiology, Children's Clinic, Gottingen, Germany.

Professor Chris. N. Barnard, Groote Schuur Hospital, University of Cape Town, Republic of South Africa, will be giving a public lecture on Cardiac Transplantation and participating in the Congress.

Postgraduate Course, Pediatric Radiology, Congenital Heart Disease will be held at Cornell University Medical College, Memorial Hospital Auditorium, 444 East 68th Street, New York City, N. Y., from April 25 to 27, 1968. Registration fee $75.00. Inquiries to Herman Grossman, M.D., Department of Radiology, New York Hospital-Cornell Medical Center, 525 E. 68th St., New York, N. Y. 10021.

The Sixth Biennial Congress of the Southern Africa Cardiac Society will be held in Johannesburg, Republic of South Africa, from Aug. 5 to 8, 1968.

It is proposed that part of the program will consist of symposia. Delegates will be asked to submit papers, the titles of which must reach the Honorary Secretary, Dr. W. F. Scott, 903, Medical Towers, Jeppe St., Johannesburg, Republic of South Africa, before Feb. 19, 1968, and the summaries by April 1, 1968. A social program for delegates and their wives is to be arranged.

The following is the program of proposed symposia:

1. *Mitral valve disease*
   - (a) Mitral valve replacement — *Dr. A. G. Morrow*
   - (b) Papillary muscle dysfunction — *Prof. G. E. Burch*
   - (c) Surgical treatment of pure severe mitral incompetence — *Dr. P. Marchand*; *Prof. C. N. Barnard*
   - (d) Local results of mitral valve replacement — *Dr. J. C. van der Spuy*; *Dr. L. Du Plessis*

   Discussion opener: Prof. V. Schrire (for total of 1 hour)

2. *Left ventricular outflow obstruction*
   - (a) Hypercalcaemic cardiovascular disease. New clinical and experimental findings in supravalvular aortic stenosis — *Dr. A. J. Beuren*
   - (b) Surgical treatment of hypertrophic obstructive cardiac myopathy — *Dr. A. G. Morrow*
   - (c) Medical treatment of hypertrophic obstructive cardiac myopathy — *Dr. R. Tucker*
   - (d) Haemodynamic, angiocardiographic and electrocardiographic correlations in patients with congenital aortic stenosis of different location and severity — *Dr. A. J. Beuren*
   - (e) The use of homograft aortic valves — *Dr. P. Obel*

   Discussion opener: Dr. M. M. Zion (for total of 50 minutes)

3. *Less common causes of cardiovascular disease*
   - (a) Viruses and the heart — *Prof. G. E. Burch*
   - (b) Prolonged Q-T syndrome — *Dr. E. Gale*
   - (c) A hitherto not described malformation of the whole vascular system diagnosed during life, and leading to coronary death in early childhood — *Dr. A. J. Beuren*

   Discussion opener: Dr. J. Reid (for total of 40 minutes)

All visitors will be welcome

American Heart Journal

June 1968 Volume 75 Number 6

Editorial

The place of phenolsulfonphthalein (PSP) in the measurement of renal function

M. Henry Gault, M.D., C.M., M.Sc., F.A.C.P.
John B. Dossetor, B.M., B.Ch., Ph.D., M.R.C.P. (Lond.), F.A.C.P., F.R.C.P. (C.)
Montreal, Quebec, Canada

The blood urea nitrogen (BUN), serum creatinine, and intravenous pyelogram frequently do not become abnormal until more than 50 per cent of renal excretory function has been lost. By contrast, the urinary PSP test (PSPU) under the right circumstances can provide a relatively sensitive and also safe, simple, and reproducible means of measuring renal function. Of comparable sensitivity is the endogenous creatinine clearance. The ^{131}I hippuran renogram is a sensitive index of abnormality as distinct from normality, but abnormal curves are difficult to interpret quantitatively in terms of function. Each of these three latter tests has advantages and disadvantages, as do tests of urinary concentrating capacity, and frequently combinations may be done with reward.

Clearances of inulin and para-aminohippurate (PAH), even when performed under the exacting conditions of constant infusion, may be in the normal range in the presence of considerable histological abnormality. Thus, for clinical purposes these more precise but also more complex tests do not give any real advantage, even though some analytical simplification has been afforded by radioactive labeling of materials such as B_{12}, edetic acid, and sodium iothalamate, which have been used to determine glomerular filtration rate, and of hippuran, which may be used to determine effective plasma flow. Moreover, comparison of tests of glomerular versus tubular function does not often provide diagnostically significant information.

Some two dozen reports[1-4] have suggested that it is possible to estimate either glomerular filtration rate or effective renal plasma flow by methods that avoid the difficulties associated with both urine collections and periods of constant infusion. Estimation of renal clearance in milliliters per minute has usually been made following a "single shot" intravenous injection of a substance by determination of the rate of disappearance from the blood during a phase when this is considered exponential with respect to time and by calculation of the volume of distribution by back-plotting to zero time. Use of the rate of disappearance alone and expression of the result as an "index of renal function"[1] may have some advantage. Substances which have been used for "single shot" method include mannitol, inulin, thiosulfate, PAH, PSP, ^{57}Co-B_{12}, ^{131}I-sodium diatrizoate, and ^{131}I-sodium iodohippurate; use of radioactively labeled materials has lessened analytical problems and improved precision. We will

From the Departments of Medical Chemistry and Medicine, Queen Mary Veterans Hospital, and the McGill University Clinic, Royal Victoria Hospital, Montreal, Quebec, Canada.

attempt to place this type of test in perspective, using as our specific example the one designed for PSP.

PSP. Since the first report[4] over 50 years ago of the rapid excretion of PSP by the kidney, this material has been used widely to assess renal function without serious mishap. The intravenous instead of intramuscular route and fractional measurement of excretion during the first hour (starting at 15 minutes) have both enhanced the value of the test. The mechanism of tubular excretion of PSP has been reviewed. Its maximal excretory rate in man is about 30 mg. per minute per 1.73 sq. M. 50 to 60 per cent is extracted by the kidney in one circulation, and normal clearance averages 400 ml. per minute. Glomerular filtration is small compared with the amount excreted by active tubular transport. Ordinarily about 1 to 3 per cent is excreted into the bile and limited intestinal absorption occurs. Binding to albumin in vivo appears much less than the 80 per cent suggested by studies in vitro, and some PSP appears to enter cells other than kidney, liver and intestine.

PSPU. As the standard intravenous dose (6 mg.) does not yield blood levels close to 1 mg. per 100 ml., at which level a secretory saturation effect is said to appear, the usual limiting factor is the rate of delivery to peritubular capillaries, rather than tubular excretory capacity. Doses of 60 mg. or of 1 mg. per kilogram of body weight may provoke some saturation effect. Thus the test primarily reflects changes in renal plasma flow.

Accurate results depend largely upon pretest hydration, on prevention of voiding for about 60 minutes before injection, and on well-trained personnel. Errors due to retention in the urinary tract are minimized when a few hundred milliliters of urine is voided at 15 minutes, and adequate flow rates render subsequent collections more accurate.

The times most often suggested for collection of specimens are 15, 30, 60, and 120 minutes after injection. As the rate of excretion normally declines quite rapidly, the 15 and 30 minute specimens provide the most sensitive estimates of function. Repeated recirculations may result in excretion of a relatively normal amount of PSP by two hours, even when renal function is moderately reduced.[4] Representative excretion ranges and average values for normal subjects after administration of 6 mg. of PSP intravenously are as follows: 28 to 51 per cent (35 per cent) at 0 to 15 minutes, 13 to 24 per cent (17 per cent) at 15 to 30 minutes, 9 to 17 per cent (12 per cent) at 30 to 60 minutes, and 3 to 10 per cent (6 per cent) at 60 to 120 minutes.[4] The 60 mg. or 10 ml. dose provides slightly slower excretion with a lower limit of normal of 25 per cent at 15 minutes.

PSP is a weak organic acid. Its color changes and becomes accentuated as pH increases from 6.8 to 8.4. The intensity of the deep-red color produced by alkalinization is measured colorimetrically after appropriate dilution; thus analytical measurement is both very simple and precise. Bile and hemoglobin, which cause positive interference, may be removed.

Errors occur chiefly in patients who have residual urine or who are unable to cooperate. Some difficulties can be overcome by knowledge of the relationship of the 15 minute and cumulative 30 minute values at different levels of renal function, as seen in Table I, which permits construction of a series of curves.[1] If the patient fails to void 15 minutes following injection, extrapolation along the appropriate curve permits estimation of an accurate 15 minute value. With good renal function about 50 per cent of the amount of PSP excreted by 15 minutes appears 15 to 30 minutes after injection; with poor function the two amounts are roughly equal. If the 15 minute value is appreciably low relative to the 30 minute value, as occurs commonly with incomplete collections of urine, back plotting from the cumulative 30 minute value along the appropriate curve yields a more accurate 15 minute value. These corrective procedures have been previously described in detail.[11] Methods based on PSP excretion have been proposed to assess more precisely the amount of residual urine.[12]

Many of the factors that impair the usefulness of the PSPU apply also to de-

Table I. Mean values for 15 minute and 30 minute urinary PSP excretion in 5? patients considered to have normal lower urinary tracts

PSP excretion at 15 min (%)	*N in group*	*Mean 15 min. value (%)*	*Mean 30 min. value (%)*	*Ratio of 30 to 15 min. value*
30–34 9	11	32 9	49 3	1 49
25–29 9	10	27 1	42 4	1 56
20–24 9	9	23 2	38 3	1 65
15–19 9	8	17 4	28 6	1 65
10–14 9	8	13 3	23 0	1 73
0–9 9	6	5 9	11 2	1 90
Mean group ratio				1 66

*From Gault, M. H., Koch, B., MacKinnon, K. J. and Dossetor, J. B.: J. Urol. 98:434, 1968.

termination of the one hour clearance of endogenous creatinine when it is performed without catheter. Dead-space errors have much less effect on 24 hour creatinine clearance but it is difficult to obtain accurate 24 hour urine collections in many clinical situations. Errors associated with secretion of creatinine may also be important.

Plasma PSP index (PSPI). A simple test of renal function has been developed which is based on serial plasma concentrations of PSP following a single intravenous injection of 1 mg. per kilogram of body weight, thus avoiding errors associated with urine collections. The use of ³⁵S-PSP* provides a more precise methodology than that suggested previously. The index is calculated from the rate of decrease of PSP in plasma 15 to 35 minutes after injection when the rate of fall is exponential and directly related to renal function and the extrarenal loss of PSP apparently is constant at a slow rate.

Use of the PSPI obviates many problems of the PSPU test, including those associated with antidiuresis, bilirubinuria, hematuria, inaccuracy of injected dose, retention of urine in the bladder, ureters or pelvis after voiding, drainage from abnormal sites (e.g., bowel or fistulas) and poor patient cooperation. The use of indwelling catheters for the PSPU may eliminate only some of these difficulties and necessitates careful bladder washout technique. The chief disadvantage of the PSPI relate to blood-specimen collection (although only one venipuncture is necessary with a scalp-vein infusion set[1]), the greater time involved in the laboratory and the lesser accuracy with poor renal function.

Comparison of the PSPU and PSPI. The relationship of these tests to each other and to clearances of creatinine, PAH and inulin is shown in Table II. Normal values for 15 minute PSPU or PSPI almost invariably are accompanied by normal values of creatinine clearance. In cooperative patients without anatomical or functional abnormality of the urinary drainage system the 15 minute PSPU yields satisfactory results, as indicated by the high degree of PSPI-PSPU correlation. However, the PSPU as compared to the PSPI has been shown to be grossly inaccurate in patients who have retention of urine after voiding or urinary drainage from abnormal sites such as bowel or fistulas,[13] and the use of PSPI is preferable. Simultaneous determinations of both tests indicate the amount of residual urine.

When assessment of renal function is required in patients without appreciable creatinemia, the PSPI should be determined instead of the PSPU (in addition to creatinine clearance) in those patients in whom difficulty in obtaining accurate urine collections is anticipated. The PSPU yields satisfactory results in most other situations.

The PSPI and other "single shot" clearance methods. Smith reviewed the potentia

*Available from the Radiochemical Center, Amersham, England.

*Table II. Correlations of PSPI, 15 minute PSPU, and clearances of creatinine, PAH, and inulin**

Variable correlated		Regression-line equations	No. of tests	r†	SE (ml./min.)
PSPI‡	PSPU	= 0 50y + 3 75 y = 1 85 − 5 13	75	0 96	2 8§
PSPI	Creatinine clearance	= 0 12y + 3 59 y = 6 67 − 8 08	132	0 88	16
PSPU	Creatinine clearance	x = 0 18y + 6 13 y = 2 75x + 29 78	52	0 70	19
PSPI	PAH clearance	= 0 02y + 5 41 y = 32 90x − 30 00	30	0 87	64
PSPU	PAH clearance	= 0 05y + 0 62 y = 16 00x + 73 81	24	0 85	62
PSPI	Inulin clearance	= 0 10y + 6 6 y = 5 40x − 6 53	30	0 80	17
PSPU	Inulin clearance	= 0 17y + 60 y = 3 16x + 15 29	24	0 73	19

*From Gault, M. H., Kinsella, T. D., Gonda, A., and Ferguson, G. A.: Canad. M. A. J. 94:45, 1966.
†r: Coefficient of correlation.
‡PSPI: plasma phenolsulfonphthalein index; PSPU: urinary phenolsulfonphthalein test.
§Percentage of PSP dose excreted in the urine 15 minutes after injection.

errors associated with this type of clearance methodology. These will vary with the material used and the relationship of the time during which the rate of disappearance is measured to the time at which equilibrium between all compartments is reached, exclusive of changes due to renal clearance. Of the several necessary assumptions for this type of methodology, the most serious difficulties arise from the assumption that mixing throughout the volume of distribution is uniform and virtually instantaneous.[2,3] The use of venous rather than arterial samples represents a further source of error, for it is theoretically improbable that venous concentration will decline as a perfect exponential function with respect to time. Also plasma protein binding, capillary permeability, and the state of the circulation may be additional uncontrollable variables. The timing of the exponential phase may vary with pool size and renal function.

If an exponential phase is used during the time the concentration is rising in any of the compartments, continuing distribution from plasma will lead to an apparent clearance greater than that due solely to the kidney. This factor may be small under ordinary circumstances but may become important when the renal function is poor, as is the case with excretion by the liver. Thus, in two studies[1,4] on patients without renal function, the equivalent of a plasma PAH clearance of up to 100 ml. per minute has been found. In view of these several potential errors, it may be pseudoscientific to express the results of such methods in milliliters per minute clearance; the use of an index based solely on the rate of disappearance from plasma may prove to be more realistic.[1]

To date, satisfactory evidence is lacking that either glomerular filtration rate or renal plasma flow can be predicted more accurately by the single shot clearance methods than by creatinine clearance or the 15 minute PSPU when the latter tests are performed on cooperative patients who do not have urological problems. In the prediction of PAH clearance (as measured by constant infusion

technique) correlation coefficients were similar with either PSPU (Table II) or with [131]I-hippurate clearance (after single injection) That single shot methods may not be superior under optimal circumstances is also suggested by the fact that PSPI was not superior to PSPU[9] We would therefore, recommend the use of the PSPI or other single shot methods only when difficulty in collecting urine specimens is anticipated in patients whose serum creatinine values are not appreciably elevated

Preferred methods have not yet been established. The PSPI has the advantages of analytical simplicity and need not involve the use of radioisotopes. However the simultaneous estimation of both glomerular filtration rate and renal plasma flow by the injection of two materials tagged with different isotopes[15] is certainly of interest as is the possibility that an external body counting technique could become practical Once appreciable azotemia or creatinemia has developed the most useful clinical criterion remains the serum creatinine when interpreted with respect to proportional changes in BUN[1]

REFERENCES

1 Gault M H The plasma phenolsulfonphthalein index (PSPI) of renal function. I Theoretical considerations and investigative studies, Canad M. A J 94:61 1966.
2 Smith, H. W The kidney Structure and function in health and disease London, 1951 The Oxford University Press, p 57
3. Editorial Measurement of glomerular filtration-rate, Lancet 2:276, 1965
4 Blaufox, M D and Merrill, J P Simplified hippuran clearance Measurement of renal function in man with simplified hippuran clearances, Nephron 3:274 1966.
5 Rowntree, L. G. and Geraghty J T An experimental and clinical study of the functional activity of the kidneys by means of phenolsulfonphthalein, J Pharmacol. & Exper Therap. 1:579 1910.
6. Relman, A. S and Levinsky N G.: Clinical examination of renal function, *In* Strauss, M B and Welt, L. G editors Disease of the kidney Boston 1963 Little, Brown & Company p. 110.
7 Lotspeich, W D Metabolic aspects of renal function, Springfield, Ill., 1959 Charles C Thomas, Publisher pp. 124-129
8. Smith, H. W Goldring, W and Chasis H The measurement of the tubular excretory mass Effective blood flow and filtration rate in the normal human kidney J Clin Invest 17:263 1938.
9 Gault, M H., Kinsella, T D Gonda, A., and Ferguson, G. A. The plasma phenolsulfonphthalein index (PSPI) of renal function. II Correlation with other parameters of renal function and indications for use Canad. M A. J 94:68, 1966
10. Henry R. J Clinical chemistry principles and technics, New York, 1964 Paul B. Hoeber Inc pp. 893-895.
11 Gault, M. H., Koch, B and Dossetor J B. Phenolsulfonphthalein (PSP) in assessment of renal function J.A.M.A. 200:871 1967
12. Axelrod, D R. Phenolsulfonphthalein excretion for estimating residual urine, Arch. Int. Med. 117 74 1966.
13. Gault, M. H Koch, B M Kinnon, K. J and Dossetor J B. The plasma phenolsulfonphthalein index (PSPI) of renal function. III Correlation with urinary PSP excretion in assessment of urological disorders, J Urol. In press
14. Blaufox, M. D and Merrill, J P Compartmental analyses of the hippuran [131]I renogram in man, Fed Proc. 24:405 1965
15. Stokes, J M., and Ter Pogossian, M M Double isotope technique to measure renal function. Single injection technique without urine collection, J.A M.A 187:20, 1964.
16. Dossetor J B. Creatinemia versus uremia: The relative significance of blood urea nitrogen and serum creatinine concentrations in azotemia, Ann Int. Med 65 1287 1966.

Clinical communications

Activation of the normal and hypertrophied human right ventricle

Andrew G. Wallace, M.D.
Madison S. Spach, M.D.
E. Harvey Estes, M.D.
John P. Boineau, M.D.
Durham, N. C.

Most previous descriptions of ventricular excitation in man have been confined to examinations of the morphology of unipolar leads recorded from selected epicardial sites, or to an analysis of records from an intramural plunge electrode. In many of these studies, the observations did not permit a description of the sequence of epicardial activation because the tracings were obtained from an insufficient number of sites. The studies described in this report were designed to examine in detail the spread of epicardial excitation over the right ventricle in patients without right ventricular hypertrophy and in patients with congenital heart diseases which were associated with right ventricular hypertrophy. Three conditions, known to produce different types of right ventricular enlargement and different types of electrocardiographic changes, were examined. The results of this study demonstrate that the sequence of activation of the normal human right ventricle is remarkably similar to that which has been described previously in dogs. In patients with right ventricular hypertrophy, activation of the epicardial surface of the right ventricle is delayed. The degree of delay and changes in the sequence of activity appear to be related to the extent and to the symmetry of the hypertrophy.

Methods

Studies were performed on 38 patients who underwent corrective heart surgery. Seven patients with congenital aortic stenosis and with normal right ventricle pressures made up the control group in whom it was considered probable that the activation sequence of the right ventricle was normal. Also included in the study were 31 patients with right ventricular hypertrophy: 14 with tetralogy of Fallot, 5 with valvular pulmonary stenosis, and 12 with secundum type atrial septal defects. Chest x-rays, electrocardiograms (ECG's), vectorcardiograms (VCG's), and cardiac catheterization data were available on all patients.

The heart was exposed through either a bilateral anterior thoracotomy with transection of the sternum or through a median sternotomy, and the entire surface of the right ventricle could be explored under direct vision without displacing the heart. A standard limb lead of the ECG was selected for recording. Lead selection was

From the Departments of Medicine and Pediatrics, Duke University Medical Center, Durham, N. C.
This study was supported in part by United States Public Health Service grants KJ-HE 1 449, HE 08815, HTS-5309, HE-0447, and a grant from the Life Insurance Medical Research Fund.
Received for publication June 12, 1967.



Fig. 1. The technique of recording at the time of open-heart surgery. The entire surface of the right ventricle is exposed and under direct vision. The probe electrode is shown on the epicardial surface overlying the outflow tract, at a location which would correspond to position 7 on the grid diagram in Fig. 2, left panel.

based on the presence of a sharp deflection point in QRS, good amplitude, and minimal respiratory variation in contour. The surface of the heart was explored with a bipolar electrode which consists of two contacts separated by a distance of 1 mm (Fig. 1). Signals were amplified with Tektronix 122 preamplifiers, displayed on a Tektronix 502 dual beam oscilloscope and recorded on an Ampex SP-300 FM tape recorder. Recordings of the ECG and epicardial electrograms were later reproduced on a Consolidated oscillograph at a paper speed of eight inches per second.

Each point from which records were obtained was carefully located on a grid diagram of the right ventricular surface using the pulmonary valve, anterior descending coronary artery, apex, and atrioventricular groove as landmarks (Fig. 2, left panel). The nadir of the Q wave or the peak of the R wave was used as a reference point, and activation at each recording site was timed in relation to this reference point. All points were then related in time to the onset of QRS in the reference lead. This technique provided a sequential map of right ventricular epicardial excitation in which each point was timed with reference to the onset of QRS in the reference lead.

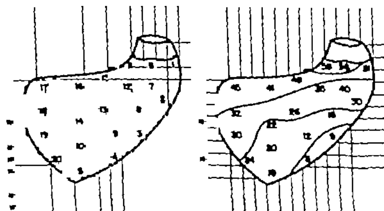
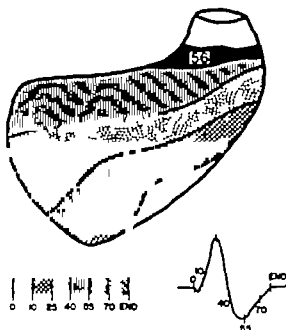


Fig. 2. Technique of depicting activation sequence of right ventricular epicardial surface. A, A grid was used to indicate the position of each of the many recording points on the right ventricle. The upper landmark indicates the pulmonary valve, the right margin indicates the position of the ventricular septum. The upper edge indicates the atrioventricular groove, and the left border is the posterior interventricular groove along the diaphragmatic surface. B, The timing of local excitation at each of the recording points is indicated by the delay in milliseconds between local activation and the onset of QRS in the reference lead. Isochronous lines were drawn to connect areas of approximately equal excitation times. The technique provides a map of the epicardial excitation sequence of the right ventricle.



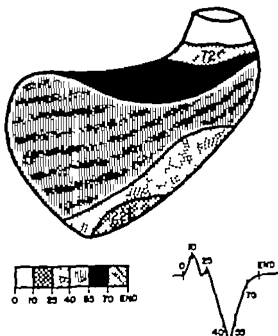


Fig Right entricular epicardial sequence in pat th ongenital aortic tenosis The pattern demo ted Fig 2 t pic l of normal ght tric lar epicardial ex tation Not the set of picardial excit tion t the trabecular zone l acent t the entricular sept m ith bsequent gration of the efront w th bend ng of the hronou l nes The area adja ent t the trio- entric la groov completed t activ tion prior t terminal excitat n of th right entricle adjacent t the pulmonic alv Activ tion times t the earliest and latest poi t re noted on the diagram These dat ere recorded in ... ars year-old child th alv lar aortic enosis, normal right en- tricular tolic pressure nd left entricular peak sy tolic pressure of 170 mm Hg

Fig 4 V lvular pulmonic stenosis. The sequence of right entricular epicardial excitation show bos was typical of the group of patients with alvular pulmonic stenosis nd symmetric hypertrophy of the right entricle The right ventricular sy tolic pressure in this patie t was 123 mm Hg The onset of epicardial excitation was delayed as compared to normals. It began on the trabecular zone with the sequence of spread occurring in normal fashion as the isochronou lines projected toward the AV groov Wa efront converged on the outflow tract ith the latest activity being recorded from beneath the pulmonic alv

(Fig 2 right panel) A complete map consisted of records from 20 to 25 points on the epicardial surface The time required for such a study averaged 15 minutes and could usually be completed while the surgeon cannulated the leg vessels for perfusion

Results

Activation of the normal right ventricle Earliest epicardial activation occurred at the trabecular zone of the right ventricle, adjacent to the septum and approximately midway between the pulmonary valve and apex. Activity appeared in this region within 10 msec after the onset of QRS in the reference lead Excitation spread outward from the trabecular zone in a radial manner so that isochronous lines bulged toward the atrioventricular groove Activation of the AV groove was completed 25 to 45 msec. after the onset of QRS and activity then converged on the region of the pulmonary outflow tract to envelop the subvalvular region In all normal patients, the outflow tract was the last area of the right ventricular free wall to be excited Activation of the entire right ventricle was completed from 4 to 59 msec after the onset of QRS. In hearts from patients with a normal right ventricle QRS activity persisted for 20 to 30 msec. after activation of the right ventricle surface had been completed. Data from one normal patient are shown in Fig 3

Activation of the right ventricle in patients with valvular pulmonary stenosis The epi-

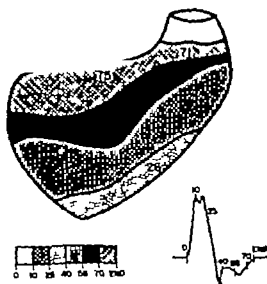


Fig 5 Secundum atrial septal defect The epicardial excitation sequence depicted box was typical of the group of pa ients with secundum type trial septal defects. These data ere recorded m nine-year-old child with 70 per cent lef to right shunt and right entricular systolic pressure of 65 mm. Hg The onset of epicardial excitation was delayed slightly ith the earliest activity occurring along the anterior septal marg near the pex Isochronous lines migrated across surface of the free wall parallel to the AV groov Terminal acti ty occurred along the atrioventricular groov

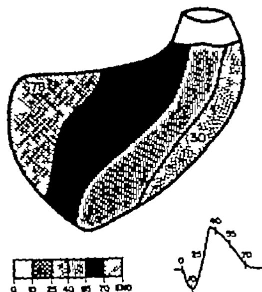


Fig 6 Tetralogy of Fallot The epicardial map illustrated Fig 5 was typical of the pattern found patient w th ventricular septal defect and in-f ndibula pulmonic tenosis (asymmetric right entricular hypertrophy) The onset of right ventricular epicardial excitation was delayed and occurred along the entire anterior septal margin. The epicardial w fronts moved across the surface perpendicular the AV groov with terminal activ tion occurring the lateral and inferior portions of the right entricle.

cardial map from one patient with pul monary valvular stenosis is shown in Fig 4. This patient had a right ventricular systolic pressure of 122 mm Hg and also had electrocardiographic evidence of severe right ventricular hypertrophy without prolongation of QRS. The earliest epicardial act ity was recorded from the anteroseptal margin near the apex Isochronous lines projected toward the atrioventricular groove and then converged on the outflow tract. The latest activity was recorded from beneath the pulmonary valve The sequence spread over the right ventricular surface and the interval between earliest and latest points on the epicard um was not strik ngly different from normal How ever the entire epicardial surface was delayed markedly The trabecular zone which is activated 0 to 10 msec. after the onset of QRS in normal patients was delayed to 22 to 30 msec and the outflow tract which is activated 20 to 30 msec. before the end of QRS n normal patients was delayed so that it contributed to the terminal QRS forces. A similar pattern of act vity was observed in all patients with valvular pulmonary stenosis.

Activation of the right ventricle in patients with secundum type atrial septal defects The map shown n Fig 5 is from a patient with a secundum type atrial septal defect. The pulmonary blood flow was 1 liters per m nute and the right entricular systolic pressure was 65 mm Hg before closure of the defect The ECG revealed an rsR complex in Lead V_1 and right ventricular h pertrophy Earliest epicar dial activity was recorded from the anteroseptal margin near the trabecular zone. Epicardial spread was directed toward the atrioventricular groove and outflow tract. In contrast to normal patients and to patients w th pulmonary alvular stenosis, the latest acti ty was recorded from the atrioventricular groove rather than from the region beneath the pulmonary alve The entire right ventricular epicardial

surface w[illegible] delayed with reference to the onset of QRS (earliest activity 26 msec after the onset of QRS).

The patient whose map is presented in Fig. 5 had a higher right ventricular pressure and more epicardial delay than was observed in most patients with secundum type atrial defects. Some epicardial delay and late activation in the region of the [illegible]oventricular groove was characteristic, however, of all the patients with secundum defects. In most of the patients with secundum defects, epicardial activity was completed prior to the end of QRS and did not contribute to the terminal portions of the R deflection [illegible] V_1.

Activation [illegible] the right ventricle in patients with tetralogy of Fallot. A map illustrating the pattern of right ventricular activation fr[illegible] one of the patients with tetralogy of Fallot (infundibular pulmonary stenosis) is [illegible] in Fig. 6. Earliest activity was recorded from the anterior septal margin. In [illegible]trast to the normal patients, there was [illegible]sentially simultaneous epicardial breakthrough over a large area at the septal margin. Isochronous lines proceeded across the free wall toward the lateral and inferior portions of the right ventricle. The last area to depolarize was the most lateral portion of the free wall along the inferior border of the atrioventricular groove. The region beneath the pulmonary valve and over the infundibular chamber was excited 40 to 50 msec after the onset of QRS which was not significantly different from that observed in patients without right ventricular enlargement. However, because of delay over the free wall and marked delay in the inferior and lateral portions of the ventricle, the outflow tract was excited early in relation to other portions of the free wall. This pattern of activation was observed in all patients with tetralogy of Fallot.

Discussion

In considering the results of these experiments, we have made certain assumptions which deserve emphasis and we have been cognizant of certain limitations to the methods of study. The patients in whom it was considered probable that the excitatory sequence of the right ventricle was normal were patients with congenital aortic stenosis. These patients had large gradients across the aortic valve and had electrocardiographic evidence of left ventricular hypertrophy. It was considered probable that the right ventricle was normal, however, since pressures recorded from the right side of the heart at the time of preoperative catheterization were normal.

The landmarks used to identify points from which recordings were made varied considerably from heart to heart. In an attempt to evaluate the reproducibility of our own observations, epicardial maps were performed in duplicate in three of the patients. The earliest and latest activity on the epicardial surface did not vary by more than ± 4 msec in any given patient and the maximal difference between individual points was ± 8 msec. By recording from multiple sites it was possible to reduce the likelihood that small errors at individual points would produce significant alterations of the map.

One of the standard limb leads was used as a reference tracing at the time of study. This lead was selected on the basis of a sharp onset and either a discrete Q wave or a sharp deflection point which could be used as a reference for timing purposes. The epicardial maps were then related in time to the onset of the QRS complex in the reference lead. The onset of QRS in any given limb lead may be delayed, however, by several milliseconds from the earliest activity which can be recorded on the body surface. This means that the interval between the onset of activity on the body surface and the onset of epicardial activation may have been underestimated by as much as 10 msec. in any given patient.[9]

Finally, we have no direct measurements of activation in the Purkinje system or of the speed of transmural spread of activation in the normal or hypertrophied human right ventricle. For these reasons, it is not possible to state with assurance that alterations of conduction in the Purkinje network did not contribute to changes observed on the epicardial surface.

Despite the limitations noted above, we believe that we have obtained data which are sufficiently precise and complete to characterize the sequence of epicardial excitation of the normal and hypertrophied

human right ventricle. Durrer and his associates, Scher and co-workers, and Boineau, Spach, and Ayers[22] have used multiple transmural electrodes to construct maps which characterized the spread of intramural activation in normal dogs, and in dogs following interruption of the bundle branches or experimentally induced right ventricular hypertrophy.[22] In the normal dog the earliest right ventricular activity is recorded from the endocardial surface near the apex at the anteroseptal margin. Excitation of the free wall occurs by endocardial to epicardial spread with the earliest area of epicardial breakthrough appearing at the trabecular zone. Epicardial activity then spreads toward the atrioventricular ring with late activation beneath the pulmonary valve. Total ventricular activation requires approximately 35 msec. in the normal dog and excitation of the right ventricle is completed by 25 msec. In right ventricular hypertrophy excitation of the free wall occurs in a normal sequence but the time required to complete activation is prolonged because of the increased muscle mass and increased thickness of the wall.[22]

The sequence of excitation of the normal human right ventricle is remarkably similar to that of the normal dog. The earliest activity is recorded at the trabecular region near the anteroseptal margin and then spreads toward the atrioventricular groove. Isochronous lines converge on the region beneath the pulmonary valve with the latest epicardial activity being recorded from the right ventricular outflow tract. Epicardial breakthrough at the trabecular region occurs early in the QRS complex and the terminal portions of the QRS complex are not attributable to activity in the free wall of the right ventricle.

In all forms of right ventricular hypertrophy which we have studied there was delay of right ventricular epicardial breakthrough and the entire epicardial surface of the right ventricle was delayed to a later portion in the QRS complex. This finding is similar to observations of experimentally induced right ventricular hypertrophy in the dog. In patients with valvular pulmonary stenosis, epicardial activity was markedly delayed. Although epicardial excitation was late at all points, the general sequence of activation recorded from the surface of the right ventricle was normal. Thus, the spread was from the trabecular zone toward the atrioventricular groove with the latest activity recorded from the outflow tract. In some patients, such as the one illustrated in Fig. 4, activity in the free wall of the right ventricle made a contribution to the terminal forces recorded from leads on the body surface.

In patients with secundum atrial septal defects, activation of the epicardial surface of the right ventricle was delayed. Earliest activity was recorded from the trabecular zone and epicardial spread was directed toward the atrioventricular groove. In contrast to normal and to patients with valvular pulmonary stenosis, the latest activity on the free wall in patients with secundum defects was recorded from the atrioventricular groove.

In patients with tetralogy of Fallot there was marked delay of activation over the epicardial surface of the right ventricle. In all of the patients whom we have studied there was a remarkable change in the sequence of epicardial activation. The earliest activity appeared consistently at the anteroseptal margin. The latest activity, however, was found laterally and inferiorly. In patients with tetralogy of Fallot the epicardial excitation spread from left to right, or from the anterior to the posterior interventricular groove. This pattern was in marked contrast to normal and to patients with comparable degrees of right ventricular hypertension due to pulmonary valvular stenosis.

The difference between the sequence of right ventricular activation in patients with pulmonary valvular stenosis and those with tetralogy of Fallot is of considerable interest. Examination of the hearts by palpation and by photographs taken at surgery revealed massive hypertrophy of the lateral and inferior portions of the right ventricular free wall in the patients with tetralogy of Fallot. All of our patients with tetralogy of Fallot had infundibular pulmonary stenosis. At the time of right ventriculotomy it became evident that the region of the right ventricular free wall between the area of infundibular stenosis and the pulmonary valve was either normal or less than normal in thickness. These anatomic findings were

surface w lelayed with reference to the onset of QRS (earliest a tivity 26 msec after the onset of QRS)

Th patient whose map is presented in Fig. had a hi her right ventricular pressur and more epicardial delay than was obser d in most patients with secundum type atrial d fects. Some epicardial delay and late a tivation in the region of the oventricular groove was haracteristic ever of all the patients w th secundum defects. In most of the patier ts with secun lun defects, ep c rdial t ity was completed prior to the nd of QRS and did not ntribute t the terminal portions of the R deflect on V

Act t on the right ventricle in patients w th tet logy of Fallot A map illustrating th patt of right ventricular activation one of the patients with tetralogy of F ll t (nfur ibular pulmonary stenosis) is n F g 6 Earliest activity was re rded from the anterior septal margin. In ntr ist to the normal patients, there essentially simultaneous epicardial breakthrough over a large area at the septal marg n Isochronous lines proceeded ross the free wall toward the lateral and nferior portions of the righ t ventricle The last area to depolarize was the most lateral portion of the free wall along the inferior border of the atrioventricular groove The region beneath the pulmonary valve and over the infundibular chamber was excited 40 to 50 msec. after the onset of QRS which was not significantly different from that observed in patients without right ventricular enlargement However because of delay over the free wall and marked delay in the inferior and lateral portions of the ventricle the outflow tract was excited early in relation to other portions of the free wall This pattern of activation was observed in all patients with tetralogy of Fallot.

Discussion

In considering the results of these experiments, we have made certain assumptions which deserve emphasis and we have been cognizant of certain limitations to the methods of study The patients in whom it was considered probable that the excitatory sequence of the right ventricle was normal were patients with congenital aortic stenosis. These patients had large gradients across the aortic valve and had electrocardiographic evidence of left ventricular hypertrophy It was considered probable that the right ventricle was normal however since pressures recorded from the right side of the heart at the time of preoperative catheterization were normal

The landmarks used to identify points from which recordings were made varied considerably from heart to heart In an attempt to evaluate the reproducibility of our own observations epicardial maps were performed in duplicate in three of the patients. The earliest and latest activity on the epicardial surface did not vary by more than ± 4 msec in any given patient and the maximal difference between individual points was ± 8 msec. By recording from multiple sites it was possible to reduce the likelihood that small errors at individual points would produce significant alterations of the map

One of the standard limb leads was used as a reference tracing at the time of study This lead was selected on the basis of a sharp onset and either a discrete Q wave or a sharp deflection point which could be used as a reference for timing purposes. The epicardial maps were then related in time to the onset of the QRS complex in the reference lead The onset of QRS in any given limb lead may be delayed however by several milliseconds from the earliest activity which can be recorded on the body surface This means that the interval between the onset of activity on the body surface and the onset of epicardial activation may ha e been underestimated by as much as 10 msec. in any given patient.

Finally we have no direct measurements of activation in the Purkinje system or of the speed of transmural spread of activation in the normal or hypertrophied human right ventricle For these reasons, it is not possible to state with assurance that alterations of conduction in the Purkinje network did not contribute to changes observed on the epicardial surface

Despite the l mitations noted above we believe that we have obtained data which are sufficiently precise and complete to characterize the sequence of epicardial excitation of the normal and hypertrophied

2. Borchardt, P R., and Groedel, F M The electrocardiogram obtained directly from the human heart, Cardiologia 9:329 1945
3 Carouso, G J Chevalier A. J Latscha, B J and Lenegre, J Epicardial electrocardiograms recorded in the course of seven cases of heart surgery Circulation 5:48, 1952.
4 Brusca, A and Magri, G. Direct epicardial electrocardiography from the exposed human heart in cases of right bundle branch block, Acta cardiol. 11:274, 1956.
5. Barbato, E., Pileggi, F Carlos Debes, A., F joka, T Magalhaes, M S. Tranchesi, J San Juan, E. and Décourt, L. V Study of the sequence of ventricular activation and the QRS complex of the normal heart using direct epicardial leads, Am. Heart J 55:867 1958
6. Barbato, E F joka, T Carlos Debes, A Pileggi, F Filho, C B de P ula Silva, P and Décourt, L. V Study of the sequence of ventricular activation and the QRS complex of the pathologic human heart, using direct epicardial leads, Am. Heart J 56:340, 1958.
7 Jouve, A., Cornol, J Torresani, J Benyamine, R., Velasque P nd Peytavy R. Epicardial leads in man, Am. Heart J 59:856, 1960
8. Durrer D Roos, J P and van Dam, R T: The genesis of the electrocardiogram of patients with ostium primum defects (ventral trial septal defects) Am. Heart J 1:612, 1966
9 Spach, M S., Silberberg W P Boineau, J P Barr R. C., Long, E. C., Gallie T M Gabor J B., and Wallace, A. G. Body surface isopotential maps in normal children, Am. Heart J 72:640, 1966.
10. Durrer D van der T eel, L. H., Berreklouw S. and van der Wey L. P Spread of activation in the left ventricular wall of the dog IV Two and three dimensional analysis, Am. Heart J 50:860, 1955
11 Scher A. M Young A C., Malmgren, A L., and Paton, R. R. Spread of electrical activity through the wall of the ventricle Circulation Res 1:539 1953.
12. Boineau, J P Spach, M. S and Ayers, C R Genesis of the electrocardiogram in atrial septal defect, Am Heart J 68:637 1964
13 Burch, G. E., and DePasquale, N P Electrocardiogram and spatial vectorcardiogram of localized myocardial hypertrophy Circulation 26:544 1962.

The effects of digitalis on atrioventricular conduction in man

Bernard D. Kosowsky, M.D.
Jacob I. Haft, M.D.
Sun H. Lau, M.D.
Emanuel Stein, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

The effect of digitalis on increasing the atrioventricular (A-V) conduction time is well established. Studies with microelectrode techniques have demonstrated that digitalis produces a prolongation of the refractory period of cells in the A-V node. It is this property of digitalis that is utilized in the treatment of rapid atrial fibrillation. Although the effect of digitalis on the human A-V node is easily seen in the presence of atrial fibrillation or flutter, its effect in normal sinus rhythms is not as readily discerned. When A-V conduction is affected to the point of producing complete heart block, 2° heart block, or the Wenckebach phenomenon, it is considered to be a manifestation of digitalis toxicity. However, it is not clear whether therapeutic doses of digitalis are normally associated with a lesser degree of block. In the present study A-V conduction time (P-R interval) was studied at identical heart rates before and after acute digitalization in normal subjects. The effect of prior atropinization was also studied in an attempt to delineate the mechanism of digitalis action.

Methods

Catheterizations of the right side of the heart were performed on eleven normal male volunteers 23 to 64 years of age. The studies were done in the supine position in a fasting nonsedated state. A No. 5 tripolar electrode catheter was positioned along the lateral wall of the right atrium under fluoroscopic and electrographic control. Two poles of the catheter were connected to a battery-powered pacer with its milliamperage set at approximately twice threshold. The third pole of the catheter was attached to the "V" lead of an electrocardiogram (ECG) in order to record a unipolar intra-atrial electrogram. A standard lead ECG (usually Lead II) was also obtained and both recordings were continually monitored. All records were taken on an eight-channel photographic oscilloscope recorder at a paper speed of 100 mm. per second. The P-R interval was measured between the atrial pacing spike and the onset of the first major deflection in the QRS complex. Measurements were made to the nearest 5 msec. (0.5 mm.)

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
This study was supported in part by United States Public Health Service Grant CD 00089-01 and by Division of Hospitals, Bureau of Medical Services, United States Public Health Service, Project Grant Py 61-44.
Received for publication June 14, 1967.
*Presently Fellow, Division of Cardiology, Georgetown University Hospital, Washington, D. C.

After recording ECG's at normal sinus rhythm the pacer was turned on at a rate corresponding to the lowest multiple of 10 above the sinus rate. Recordings were then obtained as the heart rate was progressively increased by 10 beats per minute up to a rate of 160 per minute or until dropped beats occurred. The heart was allowed to stabilize at each new heart rate for approximately one minute before records were taken. The pacer was not turned off between the different heart rates.

In eight subjects this procedure was repeated 20 minutes after the slow intravenous administration of 0.5 to 0.75 mg (0.24 to 0.34 mg per square meter) of ouabain diluted in 20 ml. of saline.

In three other subjects 2 mg of atropine sulfate were administered intravenously after the recording of P-R intervals at the various heart rates during the control state. Four minutes after the atropine was given P-R intervals were recorded at sinus rhythm and at paced heart rates to 160 per minute. Immediately following this the subjects were given ouabain as above and recordings were made 20 minutes later.

None of the subjects had ever taken digitalis preparations in the past and the subjects were taking no regular medications at the time of study.

Results

The data from all eleven subjects are presented in Table I.

In each subject in the control state atrial pacing resulted in a progressive increase in P-R interval. The P-R interval at the highest paced rate averaged 44.3 per cent above that at the lowest paced rate with a range of 13.8 to 81.2 per cent.

In several subjects atrial pacing produced a widening of the P wave as compared to that in normal sinus rhythm at a slightly lower rate. This resulted in an apparently long P-R interval as measured from the pacer spike. However the P wave duration did not change with further increases in heart rate nor with the administration of drugs. The configuration of the P wave as seen in the intra-atrial ECG did not change during the course of any study.

The administration of digitalis was accompanied by no adverse effects or subjective symptoms. No premature atrial or ventricular beats were noted and there were no alterations in the QRS or ST segments of the ECG. In most cases there was a slight decrease in the amplitude of the T wave without inversion.

Digitalis produced a decrease in heart rate in each of the eight subjects, ranging from one to 15 beats per minute with a mean decrease of 8.25 beats per minute ($P < 0.005$). The effect of digitalis on the P-R interval during sinus rhythm as measured from the onset of the P wave in the intra-atrial ECG was variable. In four subjects the P-R interval was decreased, in three it was increased, and in one it remained unchanged.

Digitalis produced an increase in P-R interval when identical paced heart rates were compared in individual subjects (Figs. 1 and 2). Of the 65 pairs of values compared in the eight subjects the P-R interval was greater after digitalis in all but seven instances. In subjects F. W. and C. W. the differences in P-R interval between the control and digitalized states progressively widened with increases in heart rate. In the other subjects the increases in P-R and heart rate were roughly parallel with and without digitalis, the values for digitalis being greater by a relatively constant amount. The mean increase in P-R interval after digitalis was 27 msec. or 11 per cent of the control P-R. The pattern of digitalis effect did not appear to vary with the subject's initial heart rate or age, or with the dose of digitalis.

The administration of atropine resulted in a progressive increase in heart rate occurring during the one-minute infusion. The heart rate reached a peak prior to the end of the infusion and remained stable at that level. In two subjects there were isolated nodal beats or short runs of nodal rhythm occurring during the infusion. In all instances these disappeared as soon as the sinus rate exceeded that of the nodal rhythm. The mean increase in heart rate in the three subjects studied was 66 per cent. With atrial pacing at identical heart rates the P-R intervals were strikingly lower after atropine. Following atropine

Table I

Subject, age (BSA*)	Dose of ouabain (mg.)	Treatment	Sinus HR† (beats/min.)	Sinus P-R interval (msec.)	P-R interval (msec.) at paced HR (beats/min.): 60	70	80	90	100	110	120	130	140	150	160
F. W., 51 (2.10)	0.50	C	58	170	210	215	220	225	240	250	290	300	W‡		
		D	53	180	220	230	250	290	350	360	380	W			
C. W., 52 (1.65)	0.50	C	77	155			210	215	270	235	235	350	W		
		D	62	165			230	235	250	330	370	W			
J. L., 56 (1.65)	0.50	C	77	145			145	145	145	150	150	155	155	160	165
		D	66	140			145	150	150	155	160	165	170	175	195
J. W., 37 (2.28)	0.75	C	76	190			190	190	200	200	205	215	225	225	
		D	75	185			200	200	210	215	215	220	220	230	
J. D., 35 (2.02)	0.50	C	64	170			185	200	215	230	240	235	245	245	260
		D	58	170			210	220	240	255	250	250	250	265	290
N. N., 52 (2.2)	0.75	C	64	195		200	210	240	280	295	355	W			
		D	58	185		30	325	300	330	370	W				
L. W., 30 (1.95)	0.50	C	59	190	210	215	220	230	240	255	280	280	285	295	295
		D	46	180	225	270	270	235	245	270	270	270	280	280	300
W. M. K., 41 (1.99)	0.50	C	68	155			205		215	220	230	240	250	270	270
		D	58	170	215		220		215	230	240	250	260	280	W
W. G., 64 (1.72)	0.50	C	62	190			235	45	250	275	280	290	300	315	
		A	95	180					185	200	205	210	210	215	
		D	95	190					200	210	215	215	220	230	
J. G., 23 (1.80)	0.50	C	64	175			185	185	190	200	205	210	215	230	250
		A	105	165						170	170	175	175	180	190
		D	106	165						1 0	180	185	195	195	200
A. L., 24 (1.97)	0.50	C	68	145		160	170	180	190	240	250	255	275	290	W
		A	121	140								145	145	150	155
		D	109	140						155	160	165	165	170	175

*BSA, body surface area in square meters.
C, control; D, after digitalis; A, after atropine.
†HR, heart rate.
‡W, Wenckebach phenomenon.



Fig. 1. Representative tracings from one subject showing the P R interval (*PR*) t four paced heart rates before and after the administration of digitalis. *ECG II* = Lead II of the standard ECG. The numbers above the tracings in the intra-atrial electrogram (IAE) represent the P R interval in msec. as measured from the atrial pacing spike (*A*) to the onset of the QRS complex. Note the progressive increase in *PR* associated w th increases in heart rate. The *PR* is longer after digitalis t each heart rat. There are no alterations in the configuration or duration of the P w es, except here it is superimposed on the previous T wave.

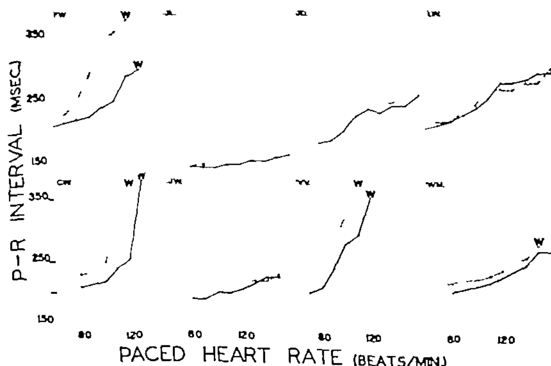


Fig. 2. The relationship of the P R interval to heart rate before and after the administration of digitalis is shown. Solid lines depict control alues. Dashed lines represent values obtained after digitalis. The occurrence of the Wenckebach phenomenon is denoted by W. I almost all instances the P R interval after digitalis is longer than that in the control state t the same heart rate.

the infusion of digitalis had little effect on the sinus heart rate. At identical paced heart rates digitalis resulted in a consistent small increase in the P-R interval. Of the 16 pairs of values compared in the three subjects, the P-R interval was greater after digitalis in 15 instances. The mean increase in P-R interval was 13 msec. or 7 per cent.

Discussion

Digitalis has been shown to have specific effects on A-V conduction. Studies in intact animals and in single cardiac fibers clearly show that digitalis produces an increase in the effective refractory period of the A-V transmission system. However, little work has appeared on the effects of digitalis on A-V conduction in man. Most previous reports are concerned with the incidence of A-V conduction disturbances seen with digitalis toxicity.[4] Fisch et al. that the P-R interval may widen as much as 0.30 second in the presence of therapeutic doses of digitalis. Friedberg and Donoso,[6] however, claim that prolongation of the P-R interval should be regarded as a sign of overdigitalization in most cases.

In attempting to study A-V conduction in the presence of digitalis one is usually faced with the problem of trying to properly define the P-R interval, especially in instances where the P wave is not prominent. Furthermore, since digitalis may result in a slowing of the sinus rate, one does not have comparable rates at which to compare the P-R intervals. It has previously been shown that increases in heart rate in the absence of augmented sympathetic activity produce a prolongation of A-V conduction time. Thus, slower heart rates are associated with shorter P-R intervals. In the presence of a slower heart rate secondary to digitalis, an unchanged P-R interval may in fact represent a relatively delayed A-V conduction time.

In the present study the P-R interval was defined as the interval between the pacing spike and the onset of the QRS complex in order to insure the greatest degree of reproducibility. In some of the subjects atrial pacing, even at low heart rates, resulted in a widening of the P wave and, therefore, a prolongation of the P-R interval as defined above. This is presumably due to the fact that the pacing electrodes were not in direct contact with conducting tissue in the atrium, thus resulting in conduction through slower atrial muscle. However, the configuration and duration of the P wave remained virtually unchanged throughout the course of any study. The increases in the P-R intervals that were noted secondary to increases in heart rate or digitalis were a result of a prolongation of the period between the end of the P wave and the onset of the QRS (Fig. 1). This corresponds to the passage of the impulse through the A-V node.* Because of the artificial increase in the P-R interval by a constant amount in those cases with P wave widening, and the inclusion in the P-R interval of atrial activation and activation below the His bundle, the percentage prolongation of A-V conduction time is somewhat underestimated.

Although digitalis had no consistent effect on the P-R interval as measured during normal sinus rhythm, a comparison of P-R intervals at identical heart rates clearly revealed a prolongation in conduction time produced by the drug. This effect was not blocked by prior vagal inhibition with atropine. It has been shown previously that intravenous atropine in the dosage used effectively blocks vagal activity for longer than one hour.[11,12] Thus, some of the effect of digitalis on A-V conduction is a result of direct action by the drug.

Previous reports have differed on the effect of digitalis on the sinus heart rate in normal subjects. Dresdale and associates,[13] studying lanatoside-C, and Selzer and associates,[1] using digoxin, showed no significant change in heart rate produced by digitalis. Ahmed and associates,[14] using a dose of one mg. of ouabain, showed a fall in heart rate in seven of nine subjects. In the present study all subjects showed a decrease in sinus heart rate.

The dose of ouabain used in this study is considered to be within the therapeutic range.[1] Indeed, there were no instances of

*A study of the effects of heart rate and drugs on the P-R interval of dogs, using His bundle electrodes, revealed that all changes which occurred were in the interval between the end of the P wave and the spike of His bundle activation.[15]

premature ventricular or nodal beats or other arrhythmias. There were no changes in the ST configuration and there were no complaints of gastrointestinal upset, visual disturbances, or headaches. Thus, therapeutic doses of digitalis affect A-V conduction in normal subjects, and the prolongation in the P-R interval is not a manifestation of digitalis toxicity. However, this effect can be clearly seen only when comparisons are made at identical heart rates before and after digitalization. These circumstances do not usually exist in most clinical situations. Since digitalis tends to lower the sinus rate, one cannot meaningfully compare the P-R intervals. In circumstances in which identical sinus heart rates are available for comparison one cannot exclude the possibility that the heart rate is being influenced by sympathetic or parasympathetic stimuli which would also significantly affect A-V conduction. Therefore, the effect of digitalis on A-V conduction is difficult to discern in the presence of normal sinus rhythm until the changes become so marked as to produce high degrees of block, at which point digitalis toxicity must be considered to be present. Even with atrial fibrillation the slowing of the ventricular rate produced by digitalis does not necessarily reflect the effect of digitalis on the A-V node. Since digitalis may increase the rate of atrial firing, there may be an enhancement of repetitive concealed conduction and a resultant decrease in stimuli getting through to the ventricles on the basis of an increase in the fibrillatory rate alone.[7] Unless the atrial rate is constant, one cannot properly assess the effect of digitalis on A-V conduction.

Summary

The effects of acute digitalization on atrioventricular conduction were studied in eleven normal subjects. P-R intervals were compared during normal sinus rhythm and at several identical heart rates produced by right atrial pacing before and after the intravenous administration of a therapeutic dose of ouabain (0.5 to 0.75 mg.). Digitalis produced a consistent decrease in the sinus heart rate with a mean decrease of 8 beats per minute. Because of this change in heart rate, the effect of digitalis on the P-R interval during sinus rhythm was variable. However, comparisons of P-R intervals at identical heart rates revealed a consistent prolongation in A-V conduction time following digitalis, with a mean increase of 27 msec. or 11 per cent. This effect was not abolished by prior atropinization. There were no premature ventricular contractions, T wave inversions, changes in the QRS or ST segments, nor any subjective signs of digitalis toxicity. Thus a therapeutic dose of digitalis can be shown to prolong the A-V conduction time in the absence of any signs of digitalis intoxication.

REFERENCES

1. Moe, G. K., and Farah, A. E.: Digitalis and allied cardiac glycosides, in Goodman, L. S., and Gilman, A., editors: The pharmacological basis of therapeutics, New York, 1965, The Macmillan Co., p. 665.
2. Hoffman, B. F., and Singer, D. H.: Effects of digitalis on electrical activity of cardiac fibers, Progr. Cardiovas. Dis. 7:226, 1964.
3. Fisch, C., Greenspan, K., Knoebel, S. B., and Feigenbaum, H.: Effect of digitalis on conduction of the heart, Progr. Cardiovas. Dis. 6:343, 1964.
4. Von Capeller, D., Copeland, G. D., and Stern, T. N.: Digitalis intoxication: A clinical report of 148 cases, Ann. Int. Med. [illegible]:869, 1959.
5. Moe, G. K., and Mendez, R.: The action of several cardiac glycosides on conduction velocity and ventricular excitability in the dog heart, Circulation 4:729, 1951.
6. Shrager, M. W.: Digitalis intoxication: A review and report of 40 cases with emphasis on etiology, Arch. Int. Med. 100:881, 1957.
7. Pick, A.: Digitalis and the electrocardiogram, Circulation 15:603, 1957.
8. Friedberg, C. K., and Donoso, E.: Arrhythmias and conduction disturbances due to digitalis, Progr. Cardiovas. Dis. 2:408, 1960.
9. Lister, J. W., Stein, E., Kosowsky, B. D., Lau, S. H., and Damato, A. N.: Atrioventricular conduction in man. Effect of rate, exercise, isoproterenol and atropine on the P-R interval, Am. J. Cardiol. 16:516, 1965.
10. Kosowsky, B., Scherlag, B., and Damato, A.: Unpublished data.
11. Craig, F. N.: Effects of atropine, work, and heat on heart rate and sweat production in man, J. Appl. Physiol. 4:576, 1952.
12. Kosowsky, B. D., Stein, E., Lau, S. H., Lister, J. W., Haft, J. L., and Damato, A. N.: A comparison of the hemodynamic effects of tachycardia produced by atrial pacing and atropine, Am. Heart J. 72:594, 1966.
13. Dresdale, D. T., Yuceoglu, Y. Z., Michtom, R. J., Schultz, M., and Lunger, M.: Effects of lanatoside-C on cardiovascular hemodynamics, Am. J. Cardiol. 4:88, 1959.

14. Selzer A Hultgren, H. N Ebnother C. L., Bradley H N and Stone, A. O Effect of digoxin on the circulation in normal man Brit Heart J 21:335 1959

15. Ahmed S Barlow, R. I S Briscoe, W. A. and M M hael, J The action of ouabain (G stroph hin) on the circulation in man and a comparison th digoxin, Clin Sc. 9 1 1950.

16. Wyckoff J nd Goldring W Intravenous injection of ouabain in man, Arch. Int. Med. 39 488 492

17. Moe G. K., and Abildskov J A: Observations on the ventricular dysrhythmia associated with trial fibrillation in the dog heart, Circulation Res. 14 447 1964

The effect of age and other factors on the early and late results following closed mitral valvuloplasty

*Laurence B Ellis M D**
Herbert Benson M.D
Dwight E. Harken M.D
Boston Mass

Since 1949 several progress reports have been made of the results, in a consecutive series, of closed mitral valvuloplasty for mitral stenosis performed by one of us (D E. H) Various preoperative factors influencing operative mortality rates and postoperative status have been correlated.[1-3] The last report was made on 1,571 patients operated upon before November 1 1961 It dealt particularly with the results five years after operation This study is concerned with the operative mortality rate and the status of patients 5 and 10 years after operation as related to cardiac disability atrial fibrillation mitral valve calcification mitral insufficiency and in particular the effect of age. The effect of preoperative systemic blood pressures on the results of surgery in these patients is the subject of another communication.

Methodology

This report extends the series to 1,817 patients operated upon prior to June 30 1966 It embraces a follow up of more than 16 years. Patients have been divided into three categories those under the age of 40 those between 40 and 59 and those 60 or older It was not feasible to break down the age groups further because such subcategories would be too small for adequate statistical analysis. Patients have been grouped according to our classification enunciated in 1952. This is similar to that of the New York Heart Association but relates more dynamically to the patient's illness. There were no patients in Group I those without symptoms. The 34 patients in Group II those with moderate but stable disability have been included for purposes of analysis with the 1 393 patients in Group III or those with progressive disability For simplicity these 1 427 patients have been designated Group III in the text and tables. Finally there were 390 patients in Group IV cardiac invalids mostly in congestive failure.

All deaths at or after operation but before discharge from the hospital were classed as "operative deaths. The follow-up method has been described previously.[4] The patients were contacted annually by questionnaires and their subjective post

From the Thorndike Memorial Laboratory Second and Fourth (Harvard) Medical Services, Boston City Hospital, The Surgical Service Peter Bent Brigham Hospital, The Thoracic Surgical Service, Mount Auburn Hospital, Cambridge, Mass., and The Departments of Medicine and Surgery Harvard Medical School, Boston, Mass.
This study was supported in part by grants 2 RO [illegible] HE 00442, [illegible] PO [illegible] HE [illegible], 5 T [illegible] HE 5244, and HE [illegible] from the National Heart Institute National Institutes of Health, United States Public Health Service.
Received for publication June 26, 1967
*Address Heart Station, Boston City Hospital, 8 8 Harrison Ave Boston, Mass 02118.

operative status and their ability to carry out daily activities were assessed. A record of complications and cardiac therapy was obtained. Many personal examinations, physicians reports, and hospital records were utilized in the assessments and to test the validity of the questionnaires. Patients moderately or markedly improved by changing one or more categories in the New York Heart Association classification were classed as *improved*. Patients were considered *unimproved* if they were but slightly improved, unchanged, or worse.

The amount of mitral valve calcification and insufficiency before the fracture were determined by the surgeon and immediately recorded. In a previous report the largest amount of mitral insufficiency recorded before or after surgery was utilized in the classification. There was no significant difference in the analysis based on only the prefracture assessment. The grading of mitral insufficiency and even of calcification by the surgeon is subject to error, yet it constitutes the most reliable available assessment.

An analysis was made of the postoperative results at 5 and 10 years. Survival curves were calculated according to the method of Berkson and Gage. In the calculation of the survival curves, patients reoperated upon were dropped from the analysis as lost to follow up at the time of reoperation. The validity of including or excluding patients reoperated upon in the survival calculation has been discussed in a previous paper.[3] The slight discrepancy between the number of dead noted in the analysis 5 and 10 years after operation and the number of dead noted by the survival-curve analysis at 5 and 10 years was due to the difference in the statistical analytical methods. The analysis at 5 and 10 years took into account only those operated upon at least 5 and 10 years ago, whereas the survival curve took into account all cases regardless of the date of operation. Also, the patients reoperated upon were included in the 5 and 10 year results, but dropped from the survival curves.

The numbers of patients in the tables in whom degrees of mitral insufficiency or of valvular calcification are shown total less than the entire series because a few records either were not available or were not sufficiently explicit to allow classification of these factors. The lack of this precise information occurs in a random fashion that does not affect the results in any category. Details of the follow up

Table I Operative deaths in terms of various preoperative findings

Category	Rhythm						Mitral insufficiency							
	Normal rhythm		Atrial fibrillation		Total		0		1+		2 3+		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age <40	11	2	22†	10	33	4	17	3	3	3	6	6	26	4
Total No. in category	514		222		736		513		107		99		719	
Age 40 to 59	15	4	66	10	81	8	25	4	19	9	22†	13	66	6
Total No. in category	361		664		1 025		598		217		176		991	
Age 60+	2	20	5	11	7	13	4	15	3	16	0	0	7	13
Total No. in category	10		46		56		26		19		7		52	

*Difference significant at the p > .01 level.
†Difference significant at the p > 0.001 level.

method and assessment have been described.[3]

Results

Patients aged less than 40 years and 40 to 59 years

THE RATE OF MORTALITY AT OPERATION The most striking difference in operative mortality rate was between Group III (less than 40 years) and Group IV (40 to 59 years) patients in both age groups (Table I) The mortality rate was 7 to 12 times higher in Group IV patients. The operative mortality rate in fibrillating patients was considerably higher than in those patients in normal rhythm This held for patients with 2 to 3+ mitral insufficiency compared to those with either 0 or 1+ mitral insufficiency It was also true in patients with 2 to 3+ valvular calcification as compared to patients with 0 or 1+ calcification. There was no significant difference in the operative mortality rate between patients with no mitral insufficiency as compared to those with 1+ and of those with no mitral valvular calcification as compared to those with 1+ Most of these differences between various subgroupings were highly significant.

When the subcategories were compared between the younger and the older groups it was seen that age itself resulted in a trend (towards increased operative deaths) that was not consistent and in general was not statistically significant.

STATUS OF PATIENTS 5 AND 10 YEARS AFTER SURGERY With the exception of one category atrial fibrillation had no discernible effect on the proportionate number of improved patients in both age groups at 5 and 10 years (Table II) The one exception was the group of patients under 40 years who were in normal rhythm at the time of surgery these did significantly less well ($p < 0.01$) at the 10 year point, as compared to those in atrial fibrillation This result is contrary to the expected trend and is unexplained

There was a progressive adverse effect of increasing degree of mitral insufficiency (0 to 2 or 3+) on the proportion of patients showing sustained improvement (Table III) This adverse effect on improvement was statistically significant ($p < 0.01$ to 0.001) in both younger and older patients, and at both 5 and 10 year points. The effect of severe mitral insufficiency appeared to be greater at the 10 year point. Such patients with 2 or 3+ insufficiency had deteriorated more than did patients in any other subgrouping only 11 per cent of the

Mitral calcification								Group					
0		1+		2 3+		Total		II + III		IV		Total	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
13	3	2	3	12	9	27	4	16	2	17†	24	33	4
465		67		128		660		664		72		736	
18	4	6	4	36†	12	60	6	20	3	61†	21	81	8
483		160		301		944		739		286		1,025	
3	15	1	10	2	9	6	11	1	4	6	19	7	13
20		10		23		53		24		32		56	

Table II. 5 and 10 year status of patients in terms of preoperative rhythm

Age (yr.)	5 years postoperative						10 years postoperative					
	Normal sinus rhythm		Atrial fibrillation		Total		Normal sinus rhythm		Atrial fibrillation		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
40												
Dead	22	7	15	4	40	7	34	16	32	13	66	13
Reoperated	25	9	21	7	45	8	68	32	31	14	97	23
Unimproved	21	7	47	15	67	11	21	11	31	14	53	13
Improved	244	77	205	72	452	74	88	41	121	57	210	49
Total	315	100	290	100	605	100	210	100	218	100	425	100
40 to 59												
Dead	25	11	68	14	94	13	34	24	95	32	131	30
Reoperated	20	8	23	5	43	6	25	1	45	14	63	15
Unimproved	47	19	92	19	141	19	36	15	65	20	84	19
Improved	164	63	296	62	462	62	50	34	85	[illegible]	140	35
Total	263	101	477	100	740	100	147	100	296	100	443	100
60 +												
Dead	1	20	10	37	11	34	1	50	3	43	4	45
Reoperated	0	0	0	0	0	0	0	0	0	0	0	0
Unimproved	2	40	4	15	6	19	0	0	2	28	2	22
Improved	2	40	13	48	15	47	1	50	2	29	3	33
Total	5	100	27	100	32	100	2	100	7	100	9	100

patients between 40 and 59 and with 2 or 3+ mitral insufficiency prior to surgery were still improved at this time.

When the degree of mitral valve calcification was related to the degree of improvement at 5 and 10 years in both the younger and older age groups, the trend was identical to that of mitral insufficiency (Table IV). In the 40- and 59-year-old category there was a progressive adverse effect of mitral valve calcification to the point where only 11 per cent were still improved at 10 years. This adverse effect upon improvement with increasing amounts of preoperative calcification was statistically significant ($p < 0.001$) in both age groups and at both 5 and 10 years.

In terms of preoperative cardiac status, there was also an adverse effect on improvement in Group IV patients when compared to Group III patients in both the less than 40 and 40 to 59 age groups (Table V). These differences were significant ($p < 0.01$ to 0.001) with the exception of the 10 year follow up in the 40 to 59 age group.

Mitral insufficiency and mitral valve calcification tend to coexist but in no regular fashion. Indeed some patients are found with marked calcification and no insufficiency and vice versa. In this current study no attempt was made to separate the two effects as was done in the earlier report.

Advancing age, comparing the less than 40 age group to the 40 to 59 age group, appeared to adversely affect improvement at 5 and 10 years in all categories. In general such differences were statistically significant.

SURVIVAL. The survival curves of the older and younger patients reflect similar trends to those of improvement (Fig. 1).

Increased age at the time of surgery

Table III *5 and 10 year status in terms of preoperative mitral insufficiency*

Age (yr.)	5 years postoperative								10 years postoperative							
	Degree of mitral insufficiency															
	0		1+		2 3+		Total		0		1+		2 3+		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
39																
Dead	19	4	11	13	9	11	39	7	34	12	15	26	16	25	65	16
Reoperated	33	7	8	10	6	9	45	8	63	21	18	23	16	25	95	22
Unimproved	36	9	5	6	19	22	60	10	37	12	3	6	11	17	51	12
Improved	343	80	60	71	40	56	45_	75	163	55	23	40	21	33	207	50
Total	430	100	84	100	84	100	599	100	297	100	57	100	64	100	418	100
40 to 59																
Dead	38	8	25	15	29	25	92	13	62	21	37	38	35	52	124	29
Reoperated	24	5	8	5	10	9	42	6	52	18	14	19	16	4	82	19
Unimproved	80	17	28	20	28	24	136	19	34	19	14	19	9	13	—	18
Improved	323	70	81	57	48	42	452	62	123	42	17	4	7	11	167	34
Total	465	100	142	100	115	100	722	100	291	100	7[illegible]	100	67	100	430	100
60+																
Dead	3	21	4	33	3	75	10	33	1	1	1	100	2	100	4	45
Reoperated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unimproved	1	7	4	34	1	25	6	20	3	50	0	0	0	0	2	22
Improved	10	72	4	33	0	0	14	47	2	33	0	0	0	0	3	33
Total	14	100	12	100	4	100	30	100	6	100	1	100	2	100	9	100

adversely affected survival in all categories with the one exception of the 5 year survival of the Group IV patients (Fig 1).

REOPERATIONS The reoperation rate of the total series up to age 60 was 7 0 per cent at 5 years and 21 per cent at 10 years. There was some variation within categories, but this showed no consistent trend of one parameter influencing reoperation more than others. Age affected the reoperation rate. Older patients had a lower reoperation rate

Patients aged 60 years and over The group of 56 patients 60 years and over at the time of surgery is too small to permit a statistical analysis particularly when broken into subgroups. In general the same trends were evident that were present in the patients between 40 and 59 Normal sinus rhythm did not appear to confer any beneficial effect on the operative mortality rate but there are only 10 patients in this category Moreover there were so few patients with well-marked mitral insufficiency and mitral calcification that it was impossible to determine adverse effect. The most important factor affecting operative mortality rates in this older group as in the younger groups was the degree of cardiac disability since there was only 4 per cent of deaths of patients in Group III as compared to 19 per cent of deaths in those classified as Group IV In general, the over-all mortality rate of these patients did not differ greatly from patients between 40 and 59

The same trends were true of the 5 and 10 year results in the over 60 age group as in the younger age groups. The results were not statistically different from those in the 40 to 59 age group in the groups as a whole and when broken down into sub-

Table IV. 5 and 10 year status in terms of preoperative mitral calcification

Age	5 years postoperative								10 years postoperative							
	Degree of calcification															
	0		1+		2-3+		Total		0		1+		2-3+		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 40																
Dead	15	5	1	2	15	15	31	7	31	12	0	0	23	31	64	15
Reoperated	27	7	4	8	14	14	45	8	63	21	7	33	25	31	87	21
Unimproved	31	8	6	17	17	16	54	10	32	12	4	19	16	13	46	11
Improved	313	80	35	73	67	65	405	75	145	55	10	45	20	25	175	45
Total	399	100	45	100	103	100	540	100	265	100	21	100	49	100	387	100
40-59																
Dead	31	8	13	11	44	21	88	13	45	22	13	27	43	40	121	31
Reoperated	13	4	4	3	1	12	41	6	34	15	12	21	30	26	78	19
Unimproved	64	15	16	14	44	22	124	15	45	20	9	16	15	13	69	17
Improved	254	70	84	72	93	45	431	63	96	43	20	39	13	11	129	33
Total	362	100	117	100	203	100	684	100	223	100	58	100	118	100	395	100
60+																
Dead	5	30	0	0	5	45	10	33	1	50	0	0		67	3	41
Reoperated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unimproved	3	23	1	17		15	6	20	0	0	1	50	1	33	2	25
Improved	5	35	5	83	4	37	14	47	1	50	1	50	0	0	2	25
Total	13	100	6	100	11	100	30	100	2	100	2	100	3	100	7	100

groups comparing those in normal rhythm and those in atrial fibrillation comparing patients with differing degrees of preoperative disability and comparing those with and without mitral insufficiency and calcification.

Discussion

The results of the extended study are generally consistent with those previously reported by us and others, with the notable difference that our previous analysis did not indicate that age was an important factor in the 5 year results. This 10 year study of numbers adequate for statistical analysis finds that age is very important. The patient's preoperative cardiac disability the presence of mitral insufficiency and valve calcification are cardinal factors in influencing operative mortality rates and in continued improvement at 10 years. Atrial fibrillation adversely affected operative mortality rates, but not long term results. Poor results evident at 5 years become even more conspicuous at 10 years.

That more reoperations were performed in the younger age group may reflect their greater surgical acceptability. It is probable that reoperation would have been more common in patients with insufficiency and calcification if good open-heart correction and prostheses had been available throughout the follow-up period. Prosthetic valves have been available only since 1961.

A total of 56 patients 60 and over at the time of surgery are included to contest the popular misconception that such advanced age contraindicates mitral valvuloplasty. True, such patients have a higher incidence of degenerative heart

Table V. 5 and 10 year status of patients in terms of preoperative cardiac status

Age	5 years postoperative						10 years postoperative					
	Group											
	II + III		IV		Total		II + III		IV		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 40												
Dead	30	5	10	19	40	7	53	14	13	31	66	15
Reoperated	40	7	9	18	49	8	81	21	16	38	97	23
Unimproved	64	12	3	6	67	11	53	14	2	5	55	13
Improved	423	76	29	57	452	74	190	41	11	26	210	49
Total	557	100	51	100	608	100	366	100	42	100	475	100
40 to 59												
Dead	55	10	30	20	94	13	75	25	44	30	131	30
Reoperated	28	5	17	9	43	6	55	18	25	19	83	19
Unimproved	103	19	38	20	141	19	66	22	19	13	84	19
Improved	362	66	100	51	462	62	104	35	41	29	145	33
Total	546	100	194	100	740	100	299	100	144	100	443	100
60+												
Dead	3	21	6	43	11	34	0	0	4	50	4	45
Reoperated	0	0	0	0	0	0	0	0	0	0	0	0
Unimproved	4	29	2	11	6	19	0	0	2	25	2	22
Improved	7	50	8	44	15	47	1	100	2	25	3	33
Total	14	100	18	100	32	100	1	100	8	100	9	100

disease and other adverse factors that compromise surgery and long term results. However the operative risk in the patients over 60 was no greater than in younger persons with comparable disability. It is of interest that nearly 50 per cent of the patients over 60 who survived operation were significantly improved at the end of 5 years and that one third of them remained improved for 10 years. It is of special interest that more than half of those surviving operation were Group IV patients before surgery. Such salvage of terminal cardiac patients is indeed worthy of note. It indicates that in properly selected older patients mitral valvuloplasty is worthwhile.

The above results help distinguish patients who will do well or poorly after *closed* valvuloplasty. No such guidelines exist for open correction of stenosis and valve replacements. Different operative procedures and prosthetic devices, relatively small series, and the absence of the long follow up preclude adequate statistics for operative mortality rates or long term results of open corrections. Conjoint studies from many clinics might contribute to adequate statistical analysis. The difficulty of standardizing patient and care factors in multiple centers is awesome and such published studies for open correction of acquired valvular disease are wanting. Dubious, even false, concepts are put forward in publications based more on clinical "hunches," wishful thinking and enthusiasm than valid scientific analysis.

Clinical perspective must be maintained. While patients with mitral insufficiency or calcification do less well some 55 to 58

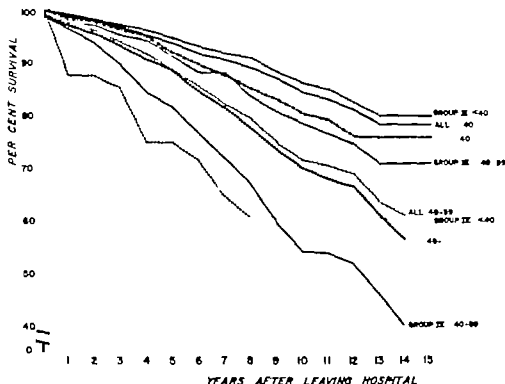


Fig. 1. Comparison of various subgroups of patients who have undergone mitral valvuloplasty. AF, Atrial fibrillation. The curves represent the follow-up of those patients who survived mitral valvuloplasty. Increased age at the time of surgery, with the exception of the five year survival in the Group IV patients, adversely affected survival. The survival curves, within each age group, reflect a slight adverse affect of atrial fibrillation at the time of surgery and marked adverse affect of the Group IV category at the time of surgery.

per cent under age 40 are still significantly improved after 5 years and ¼ to ⅓ remain improved after 10 years following mitral valvuloplasty. Of the patients with calcification or insufficiency of 2 to 3+ magnitude in the 40 to 59 age group, 42 to 45 per cent of those who survive operation are improved after 5 years; however, the deterioration of these patients at 10 years is great, with little more than a tenth of them improved. Of course these statistics do not take into account the patients reoperated upon who have been classed in the unimproved group. Many of these patients have been greatly helped by the second operation; thus the whole view of patients 10 years after surgery should include these.

Presently there is great enthusiasm for open correction of mitral stenosis and also for valve replacement, yet valid analysis needs much time and large numbers. Such evaluation must include the many patients who have suffered late complications, such as paravalvular insufficiency and embolization from the prosthesis. It should also include the late over-all clinical and hemodynamic status of the patients. Recently a discoid mitral valve prosthesis has been developed. Patients in whom this has been inserted have shown remarkable improvement in the hemodynamic status during the first few days following surgery.[7] With improvement and simplification of technical procedures, including better total body perfusion to support the brain, liver, and kidneys, better myocardial support at operation, improved valves, and better control of thrombosis, there is much promise in open heart surgery, but this promise must be buttressed by accurate and adequate data.

Summary

A report is made of a consecutive series of 1,817 patients with predominant mitral

stenosis operated by closed mitral valvuloplasty between 1949 and June 30 1966 with a follow up since operation Particular attention was paid to the influence of various factors on the operative mortality rates and the results at 5 and 10 years after surgery Severe disability (Group IV) atrial fibrillation moderate to marked valvular calcification or insufficiency all adversely affected operative mortality but the effect of age per se was not in general statistically significant. The same factors which adversely affected operative mortality also militated against good results at 5 and 10 years with the exception of atrial fibrillation In addition, advancing age adversely affected the results. A group of 56 patients 60 years and over at the time of surgery showed, in general the same trends as patients 40 to 59 years old. The present study delineates those patients that can be expected to do well or poorly after closed mitral valvuloplasty and hence sets up guidelines for studies of patients operated by open techniques and valve replacement. Until it can be clearly demonstrated that such open operations can be done as safely and the late results are better closed mitral valvuloplasty remains the operation of choice in properly selected patients with mitral stenosis.

We are indebted to Dr Hugo Muench of the *Department of Biostatistics* Lemuel Shattuck Hospital, Jamaica Plain Mass., for his aid with the statistical aspect of this material.

REFERENCES

1 Ellis, L. B., and Harken, D E. Clinical results in the first 500 patients with mitral stenosis undergoing valvuloplasty Circulation 11:637 1955.
2. Ellis, L. B., Harken, D E., and Black, H. Clinical study of 1,000 consecutive cases of mitral stenosis two to nine years after mitral valvuloplasty Circulation 19:803 1959
3. Ellis, L. B., and Harken, D E. Closed valvuloplasty for mitral stenosis. A twelve-year follow-up study of 1,571 patients, New England J Med. 270:643 1964.
4. Benson, H Ellis, L. B., and Harken, D E. The effect of preoperative systemic blood pressure on closed mitral valvuloplasty A study of 1,630 patients with up to 15 year follow-up, Am. Heart J (in press)
5 Harken, D E Ellis, L. B Dexter L., Farrand, R. E., and Dickson, J F III The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment, Circulation 5:349 1952.
6. Berkson, J and Gage, R. P Calculation of survival rates for cancer Proc. Staff Meet. M y Clin. 25:270, 1950
7 Dalen, J E., Matloff J M Hoppin, R. G J Evans, J G., Bhardwaj, P Harken, D E., and Dexter L. Early reversibility of pulmonary vascular disease after mitral valve replacement, Clin. Res. 25:344 1967

Experimental and laboratory reports

A point score system for the ECG diagnosis of left ventricular hypertrophy

Donald W. Romhilt, M.D.
E. Harvey Estes, Jr., M.D.
Durham, N. C.

The objective of this study is to present an electrocardiographic point-score system for the diagnosis of left ventricular hypertrophy (LVH) and to evaluate its sensitivity and specificity in a group of autopsied patients. Many criteria have been proposed through the years for the electrocardiographic diagnosis of LVH. Those criteria with a high degree of sensitivity generally have a low degree of specificity and the criteria with a high degree of specificity generally have a low degree of sensitivity. This is well documented by Allenstein and Mori (see Table I). In an effort to combine the various criteria into a usable system, Carter and Estes[2] re-examined some of the empirical criteria that have been proposed for the electrocardiographic diagnosis of LVH in order to weigh these criteria accordingly. LVH correlated significantly with QRS amplitude in the limb leads, the S wave depth in the right precordial leads, the R wave height in the left precordial leads, the ST-T segment shifts of left ventricular strain with the ST-T segment vectors opposite to the mean QRS vectors as illustrated in Fig. 1 (although this was of limited value in the presence of digitalis), left axis deviation using 0 degrees, −15 degrees, and −30 degrees, prolonged QRS duration, and leftward shift of the QRS transition zone in the precordial leads.

Morris and associates[3] have pointed out that left atrial involvement is an additional useful criterion for LVH (Fig. 2). This criterion is defined as a terminal negativity of the P wave in V 1 of 1 mm or more in depth and a duration of 0.04 second or more. This criterion has been found useful in routine interpretation of the electrocardiogram (ECG) and is regularly employed.

All the above criteria have been incorporated into a practical point-score system (Table II) for the diagnosis of LVH. The criteria and their point-score are as follows: (1) QRS amplitude (three points)—largest R or S wave in the limb leads equal to or greater than 20 mm, largest S wave in V 1 or V 2 equal to or greater than 30 mm, largest R wave in V 5 or V-6 equal to or greater than 30 mm. (2) ST-T segment (without digitalis, three

From the Department of Medicine, Duke University Medical Center, and the Medical Service, Durham Veterans Administration Hospital, Durham, N. C.
Dr. Romhilt was supported by the United States Public Health Service Training Grant No. HE-05369. This work also received support from the following grants: T12 HE-5734, and grant from the A.M.A. Committee for Research on Tobacco and Health (Dr. Estes).
Received for publication June 29, 1967.
*Fellow in Medicine.
**Professor of Medicine.

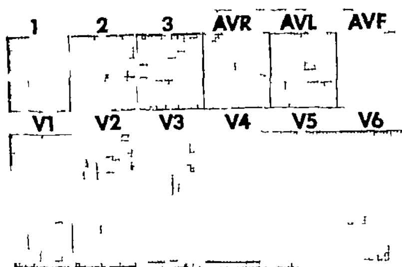


Fig. 1 ECG of 35-year-old Caucasian man with valvular aortic stenosis showing typical pattern of left ventricular strain with ST-T segment vector opposite the mean QRS vector. QRS amplitude is 30 mm. in V-6.

Table I. Allenstein's review of criteria

	Positive (%)	False Positive (%)
1. Gubner-Ungerleider	35.3	18.8
2. Katz	41.2	31.2
3. Schach, Rosenbaum, and Katz	11.8	3.1
4. Goldberger	35.3	18.8
5. Goulder and Kissane	11.8	12.5
6. Noth, Myers, and Klein	17.7	3.1
7. Wilson	94.1	78.1
8. *Sokolow and Lyon*	*88.2*	*53.1*

points with digitalis, one point)—ST segment deviation in a direction opposite to that of the main deflection of QRS, usually with a similar T wave direction as seen in Fig. 1. (3) left atrial involvement (three points)—as described in Fig. 2. (4) QRS axis (two points)—left axis deviation of −30 degrees or greater. (5) QRS duration (one point)—QRS duration equal to or greater than 0.09 second. (6) intrinsicoid deflection (one point)—time from onset of QRS to peak of R wave equal to or greater than 0.05 second in V-5 or V-6. A total score of five points is interpreted as LVH while a score of four points is interpreted as probable LVH.

Materials and methods

The hearts used in this study were the hearts of patients over the age of 15 years which have been studied during the past four years by means of postmortem coronary artery injections. This group of hearts has been selected randomly from the autopsy population but with emphasis on heart disease. These cases have been studied extensively both clinically and pathologically. Those hearts with right ventricular hypertrophy (RVH) determined on the basis of a right ventricular thickness greater than 5 mm. and a clinical diagnosis leading to RVH were excluded. Large hearts with a clinical diagnosis leading to LVH only and with marked increase in left ventricular thickness were included even if the right ventricular thickness was between 5 and 8 mm. since previous observations indicate that marked LVH may lead to secondary RVH. Also excluded were those hearts with an ECG diagnosis of complete heart block, left bundle branch block, and complete right bundle branch block. The hearts were then divided into hypertrophied and nonhypertrophied groups on the basis of Zeek's[4] criteria which evaluate normal heart weight according to body length.

The nature of the injection study, the interest of the investigators, and the selec-

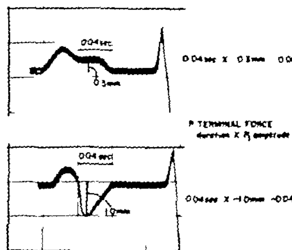


Fig 2 Calculation of the P terminal force V 1 two present t P w es from Lead V 1 The w w ided int initial nd terminal portions. The ampli de nd duration are measured separately Terminal tion multiplied by terminal amplitude = P t nal force Not that the P term nal force may positi (as upper tracing) or negative (as in wer tracing) The same measures are made for he itial portion of the P w The value is ex pressed in arbitrary nit (mm. sec). (Repri ted from Morris nd associates by permission of the American H art Association, Inc)

tion procedure weighed this group of hearts toward heart disease particularly hyper tensive and coronary artery disease. To partially balance this, and in order to provide a group of normal hearts for evalu ation of false positive diagnosis by the point score system all hearts that were of normal weight according to Zeek s criteria were selected from the autopsies at Duke Hospital in 1965 Those without ECG s and those below the age of 15 were ex cluded from the group. This provided 38 additional cases and resulted in a total group of 130 of which 90 were hyper trophied and 60 nonhypertrophied.

The ECG s all of which were obtained in the three months prior to death were interpreted according to the point score system In addition to studies of the total group the diagnostic categories of hyper tension coronary artery disease and com bined hypertension and coronary artery disease were evaluated independently with respect to the sensitivity of the point score system The hypertrophied hearts in each of these diagnostic categories were separated into those recognized as hyper trophied by the ECG (positive) and those not recognized as hypertrophied by the ECG (negative) and then compared as to average heart weight. In addition the point score system was separately con sidered in those borderline hypertrophied hearts less than 425 grams in men and 400 grams in women in comparison with those hearts greater than 700 grams.

Table II Point score system

	Points
1 Amplitude	3
2. ST T segment	
Without digitalis†	3
With digitalis	(1)
3 Left atrial involvement‡	3
4 Left axis deviation§	2
5 QRS duration‖	1
6. Intrinsicoid deflection*	1
Maximum total	13

Five points is read as LVH.
Four points is read as probable LVH.
Positive if any one of the following are present (1) largest R or S wave in the limb leads ≧ 20 mm.. (2) S wave in V 1 or V 2 ≧ 30 mm., (3) R wave in V 5 or V-6 ≧ 30 mm.
†Positive if typical ST T pattern of left ventricular strain is present (ST T segment vector shifted in direction opposite to mean QRS vector).
‡Positive if the terminal negativity of the P wave in V-1 is 1 mm. or more in depth with duration of 0.04 second or more
§Positive if left axis deviation of −30° or more is present in frontal plane.
‖Positive if QRS duration is ≧ 0.09 second.
*Positive if intrinsicoid deflection in V-5 or V-6 ≧ 0.05 second.

Results

The ECG of 52 (57 8 per cent) of the 90 hypertrophied hearts was interpreted as LVH on the basis of five points (Table

Table III Results

Diagnosis	*Positive (per cent)*	*False positive (per cent)*
Over-all	62 2	3 3
Hypertension	45 0	
Coronary artery disease	54 4	
Hypertension plus coronary artery disease	88 2	

III) In addition, four were interpreted as probable LVH on the basis of four points resulting in a total of 56 (62.2 per cent) that were positive. Of the 60 nonhypertrophied hearts, two hearts met the 5 point criteria for LVH and none met the 4 point criteria. The two false positive ECG's are interesting in that one was of a 60-year-old Negro man with severe hypertension of 220/130, an old myocardial infarction, uremia, and congestive heart failure. The ECG met the criteria of amplitude in V5 and left atrial involvement (Fig. 3) though the heart weighed only 340 grams. The second ECG is of a 74-year-old Negro woman with metastatic carcinoma of the breast, mild hypertension of 140/100, cardiac enlargement on physical examination, and a cardiac thoracic ratio at the upper limits of normal on a chest x-ray. A preoperative ECG met the criteria of amplitude in V6, left axis

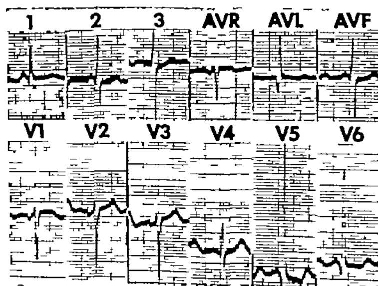


Fig. 3. ECG of 60-year-old Negro man. Six points are scored by presence of amplitude criteria in V5 and left atrial involvement. Heart weighed 340 grams.

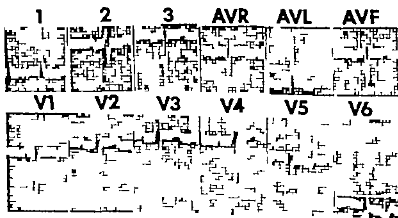


Fig. 4. ECG of 74-year-old Negro woman. Six points are scored by presence of amplitude criteria in V6, left axis deviation, and ST-T segment changes with digitalis. Amplitude criteria (R wave = 30 mm.) V6, etc. Heart weighed 230 grams.

deviation and ST-T segment changes (Fig. 4) although the heart weighed only 230 grams.

Of the 20 hypertrophied hearts with a clinical diagnosis of hypertension alone eight met the 5 point criteria and one the 4 point criteria (total of 45 per cent) for LVH. There were 22 hypertrophied hearts with a clinical diagnosis of coronary artery disease alone of which 12 (54.5 per cent) met the same criteria. There were 17 hypertrophied hearts with combined hypertension and coronary artery disease of which 15 (88.2 per cent) met the 5 point criteria for LVH. Since the point-score system was more sensitive in the presence of combined coronary artery disease and hypertension than in either of these two clinical categories separately, the average heart weights in both ECG-positive and ECG negative segments of each of these diagnostic categories were compared. Of the hypertrophied hearts due to hypertension alone the ECG negative had an average weight of 480 grams while the ECG positive had an average weight of 553 grams (Table IV). Of the hypertrophied hearts due to coronary artery disease alone the ECG negative had an average weight of 499 grams while the ECG positive had an average weight of 574 grams. In the hypertrophied hearts due to combined coronary artery disease and hypertension the two that were ECG negative weighed 350 and 630 grams (mean 490 grams) while the 15 ECG positives had an average weight of 582 grams.

There were 15 hearts which met Zeek's criteria for hypertrophy yet weighed less than 425 grams in men and 400 grams in women. In this group the ECG was diagnostic of LVH in four and probable in one other (total of 33 per cent). There were nine hypertrophied hearts with a weight greater than 700 grams and ECG's from all nine of these cases met the 5 point criteria for left ventricular hypertrophy.

The single criterion of left atrial involvement was independently evaluated as an indication of LVH since it was not included in the previous study[3] on statistical significance. Excluding those cases with atrial fibrillation this electrocardiographic criterion was positive in 40 (48.2 per cent)

Table IV. Heart weights of hypertrophied hearts

Diagnosis	ECG positive (Gm.)	ECG negative (Gm.)	Combined (Gm.)
Hypertension	553	480	531
Coronary artery disease	574	499	539
Hypertension plus coronary artery disease	582	490	571*

*This would be 538 grams if two very large hearts of 900 and 830 grams are eliminated.

of 83 hypertrophied hearts. This criterion was falsely positive in 3 (5 per cent) of 60 nonhypertrophied hearts.

Discussion

The point-score system is significantly more accurate in predicting the presence of LVH in patients with combined hypertension and coronary artery disease than in patients with either alone. This accuracy could be related to heart weight since Carter and Estes[3] in their analysis of hypertrophied hearts have previously reported a positive correlation in hypertrophied hearts between heart weight and the incidence of positive electrocardiographic parameters. The ECG positives in the combined disease group had a higher heart weight (582 grams) than the ECG positives in the single disease categories (574 and 553 grams). However, if two very large hearts of 900 and 830 grams are eliminated from the combined group the average heart weight is 538 grams. This is not significantly different from the average weight of 513 grams for the hypertrophied hypertensive hearts and 539 grams for the hypertrophied hearts with coronary artery disease. Thus, it is possible that the point-score system is more accurate in the combined group for reasons independent of heart weight.

In evaluating the specific criteria which are most often positive in the point-score system positive amplitude criteria were present in 45 of 56 (80.3 per cent). With additional points added by one additional criterion a point-score of 4 or 5 was met. A total of 11 of the 56 ECG positives were

interpreted as positive for LVH in the absence of amplitude criteria. Seven of these cases had coronary artery disease (4 in combination with hypertension and 3 alone) while only one hypertensive was in this group. Thus, criteria other than amplitude criteria may be more useful in the recognition of hypertrophy in coronary artery disease than in hypertension.

As expected the point-score system was considerably more accurate in very large hearts as compared with minimally hypertrophied hearts. This is exemplified by the incidence of 100 per cent positives in hearts over 700 grams compared to an incidence of 33 per cent positives in hearts below 425 grams in men and 400 grams in women.

We have constructed the point-score system in an effort to improve the accuracy of the electrocardiographic diagnosis of LVH. The system has a high degree of specificity; however, an improved sensitivity would be desirable. Lowering the voltage requirements to 25 mm for the S wave in V-1 to V-3 and the R wave in V-4 to V-6 only decreases the specificity without materially increasing the sensitivity. Changing the left axis deviation requirement from −30 degrees to 0 degrees did not affect specificity but on the other hand improved sensitivity by only 2 per cent.

We have evaluated additional criteria for inclusion in the point-score system. All were tentatively assigned three points and were as follows: (1) the amplitude of the sum of the greatest R plus the greatest S in the precordial leads exceeding 45 mm; (2) the presence of R amplitude in V-6 greater than R amplitude in V-5, which has been observed to have a high degree of specificity and was found to be present in 25.5 per cent of cases of LVH by Griep; and (3) the presence of a T in V-1 greater than the T in V-6. The criterion of the greatest R plus the greatest S in the precordial leads exceeding 45 mm increased the sensitivity only 1 per cent (1 case) and added two false positives to raise the false positives to 6 per cent. In the 56 hearts already interpreted as hypertrophied it was positive in 41, thus was not superior to our present voltage criteria, which were positive in 45. The criterion of a T in V-1 greater than T in V-6 increased the sensitivity by seven additional cases to 70 per cent, but also increased the false positives by six to a total of 13.3 per cent. This lack of specificity, similar to that found by Okamoto and associates,[9] caused us to discard it for use in the point score system. The criterion of the R amplitude in V-6 greater than V-5 increased the sensitivity by four cases to a total of 66.7 per cent and added only one false positive. This criterion could be added to the point-score system as a fourth voltage criterion; however, it could produce additional false positives in patients who have emphysema or other causes of RVH with a late QRS transition. These cases have been selectively excluded from this study since they frequently had RVH. At this time, we are inclined to use only those criteria presented in Table II in the point score system.

There are also circumstances in which the point-score system can be expected to have deficiencies. One example is that of mitral stenosis, in which there is a high incidence of left atrial involvement, thus scoring three points. The addition of digitalis could give ST-T segment changes resembling left ventricular strain, thus scoring one point. This would provide four points or "probable left ventricular hypertrophy." Clinical evaluation would readily reveal this error.

The advantages of this system are that the criteria are based on evaluations and scores which can be determined by inspection rather than by computation and therefore are applicable to the routine of a busy ECG reader. The criteria do not allow the diagnosis of LVH by any one criterion alone, which often leads to false positive diagnosis. Amplitude criteria are especially troublesome in this respect, particularly in younger individuals.

Summary

A point-score system is presented for the diagnosis of left ventricular hypertrophy from the ECG. It is evaluated in an autopsy series of 150 hearts with hypertrophy designated on the basis of Zeek's criteria. Using this system the ECG is positive 60 per cent of the time when LVH is present at autopsy. LVH is diagnosed in 3.2 per cent of nonhypertrophied hearts. The point-score system is significantly

more sensitive in the presence of combined hypertension and coronary artery disease than either alone.

REFERENCES

1. Allenstein, B. J., and Mori, H.: Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison, Circulation 21:401, 1960.
2. Carter, W. A., and Estes, E. H.: Electrocardiographic manifestations of ventricular hypertrophy. A computer study of ECG-anatomic correlation in 319 cases, Am. Heart J. 68:173, 1964.
3. Morris, J. J., Estes, E. H., Whalen, R. E., Thompson, H. K., and McIntosh, H. D.: P-wave analysis in valvular heart disease, Circulation 29:242, 1964.
4. Zeek, P. M.: Heart weight. the weight of the normal human heart, Arch. of Path. 33:820, 1942.
5. McPhie, J.: Left ventricular hypertrophy—Electrocardiographic diagnosis, Aust. Ann. Med. 7:317, 1958.
6. Holt, D. H., and Spodick, D. H.: The RV6: RV5 voltage ration in left ventricular hypertrophy, Am. Heart J. 63:65, 1962.
7. Griep, A. H.: Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy, Circulation 20:30, 1959.
8. Meyer, P., and Herr, R.: L'intérêt d'un Syndrome électrocardiographique TV1 > TV6 Pour le dépistage précoce de Troubles de la Repolarisation Ventriculaire Gauche, Arch. Mal. Coeur 52:753, 1959. (Quoted by Weyn, A. S., and Marriott, H. J. L.: Am. J. Cardiol. 10:764, 1962.)
9. Okamoto, N., Simonson, E., and Blackburn, H.: The TV1 > TV6 pattern for electrocardiographic diagnosis of left ventricular hypertrophy and ischemia, Circulation 31:719, 1965.

A comparison of hypoxemia and exercise electrocardiography in coronary artery disease

Diagnostic precision of the methods correlated with coronary angiography

D G Kassebaum M D
K I Sutherland M D
M P Judkins M D
Portland Ore

In general two forms of stress have been employed to provide electrocardiographic documentation of ischemic heart disease the exercise test developed by Master and co-workers[1-4] and the anoxemia test introduced by Levy and associates. These tests usually are considered positive when there is at least 1 mm ST-segment depression in one or more leads of the electrocardiogram (ECG) With the tachycardia that occurs with exercise, there is often depression of the R-ST junction (J) and an upward-slanting ST segment, wh ch is not considered as significant as flat (ischemic) ST-segment depression While some investigators[a] have suggested that significant J depression can be differentiated when the QT ratio (QTr)* is 1 08 or greater and the QX/QT ratio† is 0 50 or more others [10] have found these characteristics unreliable in evaluating J depression

Recently it has been shown that registration of the ECG during exercise is more likely to display abnormalities than the postexercise record [11,12] Recording the complete 12 lead ECG during exercise may also increase the diagnostic yield [3] While in-exercise electrocardiography has increased the percentage of positive responses in angina pectoris, it has not obviated the problem of interpretation of J depression occurring with tachycardia

The hypoxemia test obviates many of the technical problems of exercise electrocardiography The patient simply breathes 10 per cent oxygen while in the conventional supine attitude for electrocardiography No skeletal muscle activity is coupled to the ECG and the usually modest increase in heart rate and ventilation offers few of the difficulties of interpretation seen with exercise However this mode of stress electrocardiography has not enjoyed popularity because it entails special apparatus, consumes more time and may produce untoward effects unless properly monitored.[7,14]

From the Division of Cardiology and the Department of Radiology University of Oregon Medical School, Portland, Ore.
This study was supported by Program Project Grant HE-06136-06 from the United States Public Health Service and grant from the Oregon Heart Association.
Received for publication June 29 196

*QT ratio = $\frac{\text{Measured QT interval}}{\text{Corrected QT interval}}$ Corrected QT interval = $0.4\sqrt{\text{R-R interval}}$ (Bazett formula)

†QX = Interval from beginning of QRS to point where ST segment crosses isoelectric line QT = Measured QT interval.

The present study was undertaken to compare the diagnostic precision of hypoxemia and exercise electrocardiography done in the same patients who then had objective definition of the coronary anatomy by selective coronary arteriography. In so doing the accuracy of the clinical diagnosis of angina pectoris could be examined as well as the correlation of the type and degree of electrocardiographic change with the location and severity of coronary artery disease.

Methods

Subjects. Details of the clinical material are given in Table I. A total of 103 subjects was studied; both hypoxemia and graded exercise testing were done in 101 of these. Group A comprised 35 healthy medical students, house officers, and staff members who had no evidence of cardiovascular disease. None of these normal controls had coronary angiography. Group B included 25 patients in whom the diagnosis of coronary artery disease was believed improbable by the authors who saw each subject in consultation. These patients generally had atypical chest pain. Group C consisted of 43 patients with typical effort angina believed clinically to have coronary artery disease. All patients in groups B and C (total 68) had selective coronary angiography.

Hypoxemia test. This test was performed as described by Levy and associates.[4] Patients were studied no less than two hours after a meal. No patient was taking digitalis when studied or within the two weeks preceding the test. The subjects inhaled a gas mixture of 10 per cent oxygen and 90 per cent nitrogen through a mouthpiece and nonrebreathing valve. The level of hypoxemia was monitored constantly by an earpiece oximeter (Waters) calibrated against Van Slyke determinations of arterial oxygen saturation. The maximum duration of hypoxemia was 20 minutes if no chest pain, other significant discomfort, or electrocardiographic changes occurred. Some subjects became slightly light headed or noted paresthesias; rarely they experienced a mild headache. The

Table I. Clinical data and details of stress ECG tests

	A	B	C
Number studied			
Male	34	17	35
Female	1	8	8
Total	35	25	43
Age range (average)	21 51 (30)	25–63 (47)	33–66 (50)
Hematocrit range (average)	—	37 55 (46)	39–52 (46)
Hypoxemia test range (average)			
Duration (min.)	(20)	10–20 (18)	3–20 (15)
Initial S_{aO_2} (%)	90–100 (97)	92–99 (96)	88–99 (96)
Final S_{aO_2} (%)	68–90 (78)	64–90 (78)	70–95 (81)
Reduction in S_{aO_2} (%)	8–25 (19)	10–30 (19)	2 28 (15)
Initial heart rate	56–97 (72)	54–91 (75)	49–97 (75)
Maximum heart rate	57 111 (92)	64–131 (93)	45–120 (89)
Change in heart rate	−3 to +48 (+20)	−4 to +40 (+18)	−7 to +41 (+14)
Exercise test range (average)			
Maximal work level (kpm./min.)	600–1,500 (1 142)	150–1,300 (772)	200–1,000 (504)
Initial heart rate	54–97 (69)	44–94 (72)	47–97 (72)
Maximum heart rate	107 177 (149)	86–167 (136)	79–175 (114)
Change in heart rate	+35 to +123 (+80)	+21 to +122 (+65)	+3 to +98 (+43)

A, Normal controls; B, clinical diagnosis "no coronary artery disease"; C, clinical diagnosis coronary artery disease.

test was terminated if chest pain occurred if significant abnormalities (ST-T alterations) appeared in the ECG or if the arterial oxygen saturation fell below 70 per cent. Patients who experienced chest pain during hypoxemia were given 100 per cent oxygen to breathe until the pain and any electrocardiographic abnormalities disappeared. Chest pain and electrocardiographic changes, caused by either hypoxemia or exercise, disappeared within several minutes after discontinuing the stress.

Exercise test. The subjects exercised by pedaling a bicycle ergometer (Elema-Schönander) modified so that it could be operated by a person lying supine in bed. A series of graded exercise levels was performed until electrocardiographic changes or chest pain developed, until dyspnea or fatigue terminated the exercise, or until a heart rate, 85 per cent of the maximum predicted for the subject's age,[9] was reached. The subjects exercised at a given level for four minutes if neither chest pain nor electrocardiographic alterations occurred. They rested for several minutes between exercise periods until the heart rate returned to the pre-exercise level.

Electrocardiography. A standard 12 lead ECG was obtained from each resting recumbent subject prior to stress. In all cases, the resting ECG was normal. Skin electrodes (Beckman) were attached by adhesive collars to carefully prepared sites on the four extremities and six chest positions, the ten electrodes remaining in place throughout the testing period. A Hewlett-Packard (Sanborn series 350) four-channel photographic recorder was employed for registration of the ECG at a paper speed of 50 mm. per second. A special switching network permitted simultaneous registration of each of three groups of four leads, so that the complete ECG could be recorded in 15 seconds. A Hewlett-Packard (Sanborn) four-channel oscilloscope (model 569 A) was coupled to the recorder for continuous display of any selected group of four leads. A cardiotachometer (Parks Electronic Laboratory) coupled to the electrocardiograph preamplifiers, provided continuous visible and audible indication of the heart rate and rhythm. In all cases, the gain of the electrocardiographic recording system was adjusted for 1 cm. per millivolt.

Generally, the hypoxemia test was performed first and the ECG recorded whenever changes occurred and/or at the end of the period of hypoxemia. The two leg electrodes were then transferred to positions at the costal margins. These positions were found to be the most stable and free of skeletal muscle potentials during exercise of the legs. A pre-exercise control record was then taken, followed by additional records during exercise, whenever changes occurred and/or at the maximum level of exercise. Positioning the leg electrodes at the costal margins increased the wave amplitude of Leads II, III, AVR and AVF by about 50 per cent and, except for making lead axes II and AVF more nearly identical, altered the wave form very little in most cases. Post-test monitoring showed that there was no increase in electrocardiographic alterations and no new changes in the period after exercise. In all cases in which the stress provoked changes, the ECG's returned to normal within a few minutes. Subsequent repeat testing of a number of the patients, with the sequence of hypoxemia and exercise reversed, has shown no evidence of bias in the results attributable to the order in which the tests were performed.

Coronary angiography. Coronary arteriograms were done by the percutaneous transfemoral technique developed by Judkins.[11] Selective injections of 6 to 8 ml. Renografin* were made directly into the coronary artery orifices through preshaped Ducor† catheters. The injections of both the right and left coronary systems were filmed in the left lateral, 70 degrees left anterior oblique, and 15 degrees right anterior oblique positions on both overframed 16 mm. cine film at 60 frames per second and by rapid serial filming at 4 per second for two seconds and 1 per second for two seconds using an Elema-Schönander rapid film changer. To reduce distortion and avoid misinterpretation of layered contrast agent, the serial films were taken with a horizontal x-ray beam.

The three main branches of the coro-

*Renografin, E. R. Squibb and Sons, New York, N. Y.
†Ducor, Cordis Corp., 125 N. E. 40th St., Miami, Fla.

Table III. Stress ECG and coronary angiographic findings in patients with clinical diagnosis no

Subject	Sex	Age	Hypoxemia test: Maximum ST depression (mm.)	ST contour	QTr	QX/QT
M. B.	M	45	0	iso	1.01	—
I. B.	F	5	2.2 N	flat	1.13	0.80
M. B.	F	5	0	iso	1.06	—
H. B.	M		0.4 H	flat	1.10	—
K. D.	F	63	0	iso	1.09	—
W. C.	M	45	0	iso	0.99	—
J. C.	M	17	0	iso	1.09	—
I. L.	M	55	1.0 N	↑	1.00	0.57
F. M.	M	57	0	iso	1.03	—
M. S.	F	44	0	iso	0.96	—
I. H.	F	51	0	iso	1.03	—
N.	M	27	0	iso	1.07	—
C.	F	32	0.8 N	flat	1.03	0.55
	F	44	0.4 N	flat	1.09	0.77
L.	M	47	0	iso	1.06	—
I. W.	F	63	0	iso	1.11	—
D. S.	M	47	0	iso	1.03	—
H. B.	M	50	0	iso	1.06	—
F. M.	M	53	0	iso	1.08	—
B. J.	M	46	0.9 H	flat	1.10	0.56
D. H.	M	25	0	iso	1.11	—
N. H.	M	35	0	iso	1.03	—
I. M.	M	35	0	iso	1.12	—
N. D.	M	48	0	iso	1.08	—
M. O.	M	54	0	iso	1.05	—

Abbrev.: iso, isoelectric; flat, ST segment flat for ≥ 0.08; ↑, J depression with ST segment slanting upward.

had selective coronary angiography following stress electrocardiography, and minimal evidence of coronary disease was found in two cases (Table III).

Table III shows the effect of hypoxemia on the ST segment, QTr, and QX/QT ratios. The two cases found to have minimal coronary artery disease had ischemic ST depression (ST segment flat for at least 0.08 second) of 2.2 and 0.9 mm. Four patients with no angiographic evidence of coronary disease also had ST changes, with J depression of 1.0 mm. in one and ST-segment depression in the other three of 0.4 (two) and 0.8 mm. The range and the mean of the QTr and QX/QT ratios are given in Table V. The QTr was 1.08 or more in eight of the 23 normal patients and in the two with coronary artery disease. The QX/QT ratio was 0.50 or greater in the two cases of coronary disease and in three of the four normals with ST alterations.

EXERCISE TEST. Graded exercise testing was done in all of the patients in this group. Table I shows the range of exercise performed and the effect of maximum exercise on the heart rate. The same T wave reduction occurred in this group as in the normal controls, both with hypoxemia and exercise. Table III, which indicates the magnitude and location of the maximum ST changes that occurred, shows that nearly half of the patients (12 out of 25) exhibited J depression (predominantly in Leads II, III, and AVF), including the two with coronary disease. Only eight subjects had ST changes of any magnitude

coronary artery disease

Exercise test				
Maximum ST depression (mm)	*ST contour*	*QT*	*QX/QT*	*Coronary angiography*
0	iso	1 12	—	No coronary artery disease
1 0 V	↑	1 13	0 47	Attenuation anterior descending
0	iso	1 01	—	No coronary artery disease
0 5 V	↑	1 00	0 47	No coronary artery disease
0	iso	1 05	—	No coronary artery disease
1 0 V	↑	1 08	0 46	No coronary artery disease
0	iso	1 03	—	No coronary artery disease
1 4 II	↑	1 11	0 53	No coronary artery disease
1 0 II	↑	1 10	0 46	No coronary artery disease
0	iso	1 02	—	No coronary artery disease
1 2 II	↑	1 06	0 44	No coronary artery disease
0.5 V	↑	1 04	0 48	No coronary artery disease
1 0 II	↑	1 11	0 50	No coronary artery disease
0	iso	1 15	—	No coronary artery disease
0 8 II	↑	1 02	0 48	No coronary artery disease
0	iso	1 11	—	No coronary artery disease
1 0 II	↑	1 10	0 43	No coronary artery disease
0	iso	1 18	—	No coronary artery disease
0	iso	1 03	—	No coronary artery disease
1 3 II	↑	1 03	0 61	Narrowed right and anterior descending
0	iso	0 99	—	No coronary artery disease
0	iso	1 05	—	No coronary artery disease
0	iso	1 13	—	No coronary artery disease
0	iso	0 99	—	No coronary artery disease
1 0 AVF	↑	1 11	0 46	No coronary artery disease

in the chest leads, mostly less than 1 mm. J depression. None had segmental ST depression.

Table III shows the QT and QX/QT ratios for individual subjects Table V gives the range and the mean of the QT and QX/QT ratios for the group. The QTr was 1 08 or more in only one of the two subjects with coronary disease but in nearly half of those with no angiographic evidence of disease (in 11 of the 23) The QX/QT ratio was 0.50 or more during exercise of one of the two abnormals, and in only two of the 23 normals.

Patients with clinical diagnosis coronary artery disease [11]

HYPOXEMIA TEST Table I shows the clinical data, degree of hypoxemia, and effect on the heart rate in 42 of the 43 patients believed clinically to have coronary artery disease All of these subjects had selective coronary arteriography following stress electrocardiography There was no angiographic evidence of coronary artery disease in six patients who described typical effort angina (Table IV)

Table IV shows the effects of hypoxemia on the ST segment QTr and QX/QT ratios. Although two of the cases without angiographic evidence of coronary disease had no electrocardiographic changes with hypoxemia four others had ischemic ST alterations. The ST-segment depression exceeded 0 5 mm in only one case this patient's positive stress ECG is shown in Fig 2 and his normal coronary arteriogram is illustrated in Fig 3

Ten patients, with coronary artery dis-

Table IV. Stress ECG and coronary angiographic findings in patients with clinical diagnosis coro-

Subject	Sex	Age	Hyperemia test			
			Maximum ST depression (mm.)	ST contour	QTr	QX/QT
J. C.	F	43	1.0 \	flat	1.23	0.61
C. C.	M	47	0.4 \	flat	1.03	0.53
B. C.	M	56	2.4 \	flat	1.08	0.53
R. D.	M	52	0.4 H	↑	1.07	0.49
R. D.	M	50	0	iso	0.97	—
W. J.	M	41	1.3 \	flat	1.12	0.53
N. F.	M	47	1.4 \	↓	1.09	0.72
J. B.	M	66	1.0 H	flat	1.00	0.65
H. I.	F	44	0.5 \	flat	1.06	0.56
L. C.	F	43	0.3 \	flat	1.07	0.44
T. C.	M	47	0.9 H	flat	0.98	0.82
C. C.	M	61	1.3 \	flat	1.08	0.53
J. H.	F	47	—	—	—	—
B. H.	M	43	0	iso	1.03	—
T. L.	M	33	1.0 H	↓	1.06	0.78
H. B.	M	54	0.7 H	flat	1.05	0.60
H. J.	M	56	2.3 \	↓	1.06	0.76
W. M.	M	38	0	iso	1.01	—
H. M.	M	60	1.1 \	flat	1.15	0.62
A. P.	M	56	0	iso	1.10	—
I. D.	M	58	0.7 \	flat	1.13	0.6
W. M.	M	33	1.0 \	flat	1.11	0.55
M. R.	M	58	0	iso	1.12	—
R. S.	M	44	0	iso	1.08	—
G. S.	F	47	0.6 \	flat	1.16	0.51
D. S.	M	48	1.5 \	↓	1.10	0.61
G. S.	M	46	0.3 H	flat	0.97	0.63
T. W.	M	34	0	iso	1.00	—
M. W.	M	41	0	iso	1.02	—
R. Y.	M	52	1.1 \	flat	1.50	0.78
A. Z.	M	54	0.3 \	flat	1.14	0.46
G. D.	M	62	0	iso	1.03	—
H. W.	M	48	1.0 H	flat	1.00	—
V. B.	M	53	0.6 V	↑	1.05	0.35
N. H.	M	54	2.0 V	flat	1.09	0.63
C. W.	M	43	0	iso	1.00	—
M. W.	F	47	1.4 \	↓	1.03	0.72
A. O.	F	54	1.0 V	flat	1.13	0.57
G. S.	M	52	0.3 \	flat	1.02	0.46
I. B.	F	49	0.2 \	flat	1.07	—
A. D.	M	58	0	iso	1.08	—
J. H.	M	48	3.0 \	↓	1.03	0.82
F. W.	M	51	0	iso	0.97	—

Abbrev.: Iso, isoelectric flat, ST segment flat for ≥ 0.08; ↑ J depression with ST segment slanting upward; ↓ ST depression with downward slanting ST segment.

nary artery disease"

Exercise test				Angiographic evidence of coronary disease		
Maximum ST depression (mm)	ST contour	QT	QX/QT	Right	Anterior descending	Circumflex
1 5 II	flat	1 11	0 60	moderate	0	0
0	iso	1 12	—	0	0	0
1 7 V	flat	1 08	0 59	moderate	moderat	minimal
2 0 II	↑	1 03	0 50	moderate	0	minimal
0	iso	0 99	—	moderat	0	minimal
2 5 II	↑	1 18	0 52	minimal	severe	severe
3 8 V	↓	1 03	0 78	moderate	moderate	moderat
1 6 AVF	flat	1 08	0 59	sever	0	moderat
1 0 II	↑	1 04	0 48	0	0	0
0 8 II	↑	1 10	0 47	0	0	0
1 5 II	flat	1 09	0 72	moderate	moderate	moderate
1 7 II	flat	1 14	0 53	moderate	severe	moderate
2 0 II	↑	1 06	0 50	moderate	moderate	0
0 2 II	↑	1 08	—	minimal	0	0
1 4 III	↓	1 08	0 82	0	0	0
1 6 II	flat	1 08	0 73	severe	moderat	moderate
2 0 II	flat	1 11	0 78	severe	severe	severe
0	iso	1 10	0 27	0	severe	0
1 4 V	flat	1 17	0 56	moder te	moderate	moderate
0 2 II	↑	1 06	0 51	0	moderate	0
1 0 AVF	flat	1 11	0 53	moderate	severe	minimal
1 6 V	↑	1 18	0 57	moderate	0	moderate
0	iso	1 18	—	moderate	minimal	moder te
0	iso	1 08	—	0	minimal	minimal
0 5 V	flat	1 15	0 51	severe	0	severe
4 2 II	↓	1 03	0 80	severe	severe	moderate
0 3 AVF	flat	1 12	0 48	minimal	severe	minimal
0	iso	1 04	—	0	0	0
0 3 II	↑	1 06	0 33	minimal	severe	moder te
0 5 II	↑	1 17	0 44	sever	moderate	moderat
1 0 V	↑	1 07	0 49	moderate	moderat	moderate
2 3 II	flat	1 22	0 76	severe	0	moderate
1 0 II	flat	1 03	0 50	severe	severe	severe
1 3 II	↑	1 13	0 50	sever	0	moderate
2 0 II	fla	1 09	0 50	modera t	0	minimal
1 0 II	↑	1 00	0 30	minimal	moderate	moderate
2 0 II	↓	1 09	0 72	modera t	moderat	sever
1 0 II	fla	1 10	0 50	minimal	moderat	moderate
2 8 II	flat	1 16	0 67	severe	severe	moderat
0 6 AVF	↑	1 14	0 47	minimal	0	0
0 2 V	fla	1 03	0 47	moderate	minimal	mi mal
2 8 V	↓	1 07	0 81	moderate	sever	severe
3 5 III	↑	1 03	0 58	0	0	0

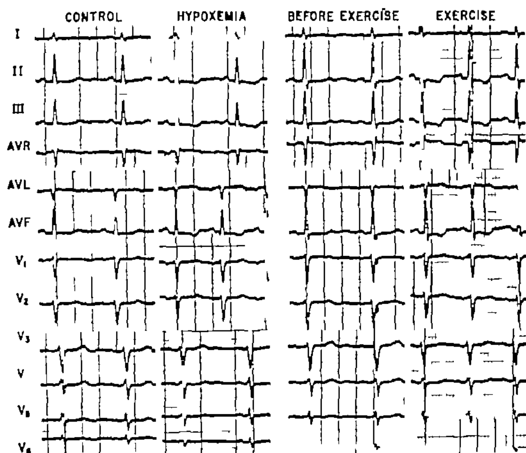


Fig. 2. Effect of hypoxemia and exercise on the ECG of a patient (T. L.) with typical effort angina, but normal coronary arteriogram (see Fig. 3). Both hypoxemia and exercise produced typical "ischemic" ST-segment depression and T-wave inversion. Leads II, III, and AVF.

ease ranging from minimal to severe had no ST-segment alterations with hypoxemia (Table IV). A total of 26 subjects out of a total of 36 in this group with angiographically proved coronary disease had ST changes with hypoxemia (Table IV). In all but two cases this was "ischemic" ST depression: the ST segments depressed and either flat for at least 0.08 second or slanted downward into biphasic and predominantly negative T waves (see Fig. 2).

Table V gives the range and the mean of the QTr and QX/QT ratios. A QTr of 1.08 or more was not found in any of the six normal patients, while the QX/QT ratio was 0.50 or greater in three of these. In over half of those with angiographic evidence of coronary disease the QTr was 1.08 or more (19 out of 36), the QX/QT ratio was 0.50 or more in 22 of these subjects. Looked at the other way around, the QTr was normal in 47 per cent and the QX/QT normal in 39 per cent of patients with proved coronary disease.

EXERCISE TEST. Exercise electrocardiography was done in 43 patients including the same 42 having hypoxemia tests. Table I shows the range of exercise performed by this group and the effect on heart rate. In most cases there was some reduction in T wave amplitude with exercise, regardless of whether there was an ST change. In a number of cases of ST depression, particularly when the ST segment slanted downward, the T wave became biphasic or inverted. In no case was there alteration in the polarity of the T wave without ST-segment depression.

Table IV indicates the effects of the maximum level of exercise performed on

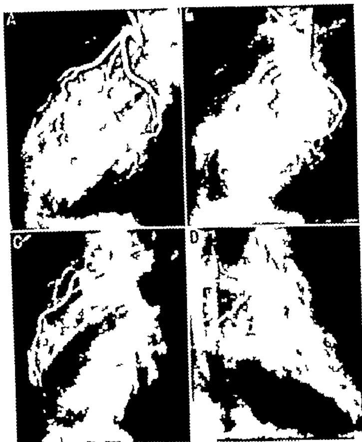


Fig. 3 Coronary arteriogram of the patient (T L.) whose stress ECG is illustrated in Fig The normal anterior descending and circumflex branches of the left coronary are shown A and B of the normal right coronary artery in C and D

the ST segment QTr and QX/QT ratios. As with hypoxemia two of the six patients without angiographic evidence of coronary disease had no electrocardiographic alterations with exercise while four exhibited ST changes, but of the J depression type

Four patients with coronary disease had no ST-segment alterations with exercise.

Of the total of 37 patients in this group with angiographically documented coronary disease 33 had ST alterations with exercise. Table IV shows that there was J depression with upward-slanting ST segments in 12 of these and ischemic ST depression in 21 cases The maximum ST alterations occurring with exercise were seen in Leads II III and AVF in contrast to the hypoxemia test in which the major changes appeared in the chest leads Since there is a chance that the two tests did not sample equally the distribution of ST changes was analyzed with regard to those occurring in Leads II III and AVF and those seen exclusively in the chest leads. If only ST alterations in the chest leads were considered there were more false-negative exercise tests and fewer instances of junctional R ST depression With hypoxemia, on the other hand, the number of false negatives increased considerably when only ST changes in Leads II III and AVF were considered.

Most patients with moderate or severe disease of two or more major coronary arteries had significant ST changes in both the hypoxemia and exercise test (Figs. 4 and 5) An occasional case with no electrocardiographic alterations with hypoxemia showed typical ischemic ST-T changes with exercise (Figs. 6 and 7) On

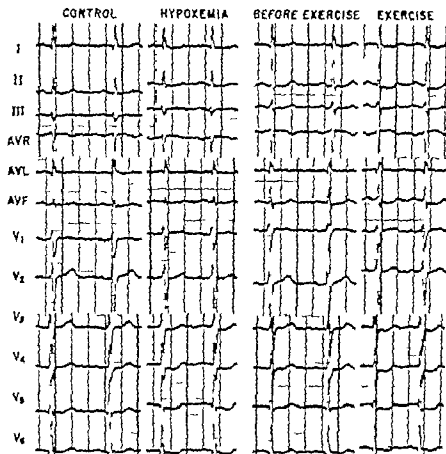


Fig. 4. Effect of hypoxemia and exercise on the ECG of a patient (J. H.) with typical effort angina and severe arteriosclerotic disease involving both major coronary arteries (see Fig. 5). Both hypoxemia and exercise produced ischemic ST segment changes most marked in the chest leads.

the other hand, some subjects with mixed J depression and localized ST segment depression with exercise showed unequivocal and generalized ischemic ST-T alterations with hypoxemia (Fig. 8). Generally, patients with minimal and moderate disease of one or more vessels had less marked ST changes with exercise and smaller or no ST alterations with hypoxemia.

There was little correlation between the location of the coronary disease and the electrocardiographic leads in which major changes occurred. In general, disease involved major branches of both right and left coronaries, with a slight preponderance of right coronary disease. When the disease was more marked in the right coronary, ST changes with exercise occurred predominantly in Leads II, III, or AVF. However, Leads II, III, and AVF also exhibited the major electrocardiographic changes during exercise when disease was severest in the left coronary artery.

The hypoxemia test, on the other hand, showed the major ST changes more often in the chest leads, regardless of whether coronary disease involved the three vessels about equally, there was a preponderance of disease in the right coronary artery, or the disease involved primarily the left coronary artery.

Discussion

The accuracy of hypoxemia electrocardiography was compared with that of exercise electrocardiography in the diagnosis of coronary artery disease. In order to define the type of electrocardiographic changes that occur normally under the influence of these stresses, the response

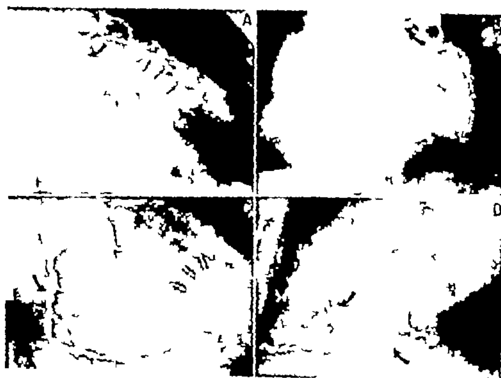


Fig. 5. Coronary arteriogram of the patient (J. H.) whose stress ECG is illustrated in Fig. 4. The left coronary artery is severely diseased (A and B). The anterior descending branch is completely occluded at its origin (upper large arrow, A). The circumflex branch of the left coronary artery is completely occluded about 1 cm. distal to its origin (lower large arrow, A). Fragments of the circumflex and anterior descending systems are opacified via numerous small collateral vessels (small arrows, A). There is irregularity throughout the right coronary system, with two major areas of narrowing (large arrows, C and D). The distal fragment of the anterior descending branch of the left coronary is filled via numerous septal collaterals (small arrows, C).

was examined in two groups of subjects without coronary artery disease. One group comprised 35 asymptomatic subjects with no clinical evidence of disease. The other group consisted of patients whose selective coronary arteriography showed radiographically normal coronary arteries. This second group totaled 29 patients. 23 of these were believed to have no coronary artery disease on clinical grounds, but the other six were thought to have angina pectoris although coronary arteriography showed no evidence of coronary disease.

The electrocardiographic response to hypoxemia was similar in the two groups of subjects without coronary artery disease. Three of the 35 normal controls had ST changes with hypoxemia; in all cases greater than 0.5 mm. ST-segment depression. Of the 29 patients without angiographic documentation of coronary disease eight had ST changes with hypoxemia, and three of these (10 per cent) had ischemic ST-segment depression greater than 0.5 mm. J depression was rare with hypoxemia.

There were 39 cases of coronary artery disease documented by coronary arteriography. Hypoxemia produced ischemic ST-segment depression of at least 0.5 mm. in 26 of these (67 per cent), ischemic ST depression < 0.5 mm. in one, J depression twice, and no electrocardiographic change in 10 (26 per cent).

The majority of subjects exhibited ST alterations with exercise. A total of 29 of the 35 normal control subjects (83 per cent) had ST depression (almost exclusively junctional) in a nearly Gaussian distribution around a mean of about 1.0 mm. A total of 14 of the 29 patients (48 per

I Eff h on the ECG of III B h t pa l effort angina and angio- k coronary artery disease (see Fig 7). Although there were no significa t ECG h sed t pa l bcm ST E ha ges



Fig 7 Coronary arteriogra of the p t III B whose tres ECG is illustrated Fig 6. The top arrow in *A* points t the marked narrow g of he left oronar rt ermedia ly prior t he branching of the circumflex and anterior descending es he lower rrow ndic t stenosi the origins of these branches. There is diffuse narrowing throughou both he erior descending nd irc mflex arteries and a diffuse network of fine septal nd left ventricular br he arising primarily from the diagonal and anterior descending arteries. In *B* is seen an aneurysmal dilatat on in the proximal part of the righ coronary artery and areas of almost complet (upper arrow) and complet (lower arrow) occlusion The essel below the lower arrow is superimposed in this projection, but is not in the same plane w th he occluded branch of the right coronary artery

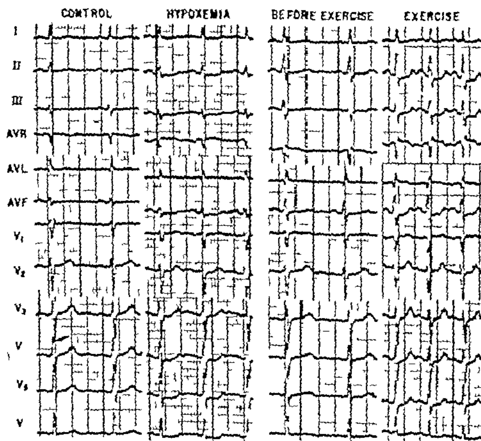


Fig. 4 Effect of hypoxemia and exercise on the ECG of patient (N. H.) with typical effort angina and angiographic evidence of moderate right coronary disease and minimal disease of the circumflex branch of the left coronary artery. In the exercise ECG Leads II, III, and AVF show ST-segment depression although the segments slant upward slightly in Leads II and AVF and are typically "ischemic" only in III. The chest leads show only J depression with exercise. With hypoxemia unequivocal "ischemic" ST-segment depression occurs in Leads II, III, and AVF and in most of the chest leads.

cent) with angiographically normal coronaries also had ST changes of the same nature. In the group of patients with the clinical diagnosis "no coronary disease" there was no case of "ischemic" ST depression with exercise.

To reduce the number of false-positive exercise tests among normals it would seem reasonable to ignore R ST junctional depression and consider significant only "ischemic" depression of the ST-segment of at least 1 0 mm, which occurred in only two of the normal controls (6 per cent) and one of the angiographically documented normals (3 per cent). Of the 39 subjects with documented coronary artery disease exercise produced J depression in 14 (36 per cent) and "ischemic" ST-segment depression in 21 (≥ 1 0 mm in 18 of these, or 46 per cent of the total). In four cases with coronary disease there were no ST changes induced by exercise.

Ignoring ST changes which occur in greater number in Leads II, III, and AVF does not resolve the problem because while the number of cases of both junctional and segmental ST depression is reduced, the number of false negative tests increases appreciably.

It would seem necessary, however, to insist on "ischemic" ST-segment depression of at least 1 0 mm as the only valid criterion of the exercise test which confidently distinguishes those with dis-

Table V. Changes in ST segment, QT, and QX/QT ratios with stress electrocardiography

	A		B		C	
	Hypoxemia	*GXT*	*Hypoxemia*	*GXT*	*Hypoxemia*	*GXT*
No. [illegible]						
Normals	35	34	23	23	6	6
Coronary disease*	0	0	2	2	36	37
Total	35	34	25	25	42	43
With ST changes						
J depression	1	26	1	12	2	12
Ischemic ST changes	2	3	5	0	28	21
Total	3	29	6	12	30	33
QTr ratio						
Normal (range)	0.92–1.18	0.92–1.18	0.96–1.12	0.99–1.13	1.00–1.07	1.04–1.12
(Mean ± S.D.)	(1.05 ± 0.06)	(1.01 ± 0.06)	(1.03 ± 0.04)	(1.07 ± 0.05)	(1.05)	(1.08)
Coronary disease	—	—	1.10, 1.13	1.00, 1.03	0.97–1.16 (1.07 ± 0.09)	0.99–1.22 (1.09 ± 0.05)
QTr ≥ 1.08						
Normals	15	10	8	11	0	3
Coronary disease	—	—	2	1	19	23
QX/QT ratio						
Normals (range)	0.50–0.85	0.38–0.96	0.57–0.77	0.44–0.53	0.44–0.78	0.50–0.82
(Mean ± S.D.)		(0.51 ± 0.10)		(0.47 ± 0.03)		
Coronary disease	—	—	0.56, 0.80	0.47, 0.61	0.35–0.82 (0.60 ± 0.11)	0.27–0.81 (0.56 ± 0.13)
QX/QT ≥ 0.50						
Normals	3	16	3	2	3	2
Coronary disease		—	2	1	22	27

A, Normal controls; B, clinical diagnosis: no coronary artery disease; C, clinical diagnosis: coronary artery disease.
*Coronary disease assumed absent in asymptomatic control subjects who did not have coronary arteriography.

from normals. Clearly, this is a compromise which resulted in misdiagnosis by exercise electrocardiography of over half of the patients with coronary artery disease. On the other hand, an exercise test in which no electrocardiographic change occurred correlated 90 per cent with normal coronary arteriography.

In contrast to the exercise test, the hypoxemia test was easier to interpret on account of less variability in the type of ST change produced. Using as the criterion of positivity an ischemic ST segment depression of at least 0.5 mm., the incidence of false-positive tests was scarcely larger than with exercise (about 10 vs. 6 per cent), and the true positive responses correlated with angiography in 67 per cent of the cases.

In this study, the QTr and QX/QT ratios were not useful in refining the diagnostic accuracy of either mode of stress electrocardiography. In the first place, the variation of these measurements within groups was wide. Furthermore, one or both ratios were abnormal in almost half of the subjects without coronary artery disease. These results confirm the observations of others[28] and indicate the unreliability of these characteristics in evaluating ST depression.

This study, employing coronary artery visualization, also permitted an appraisal of the accuracy of the clinical diagnosis

in the 68 patients having angiography. There were 8 per cent false negative clinical diagnoses of coronary artery disease and 14 per cent false positive diagnoses. Obviously this assumes that the ultimate determinant of the existence of coronary artery disease is angiography. While this must be considered the most precise diagnostic technique currently available, it is indeed possible that some of the subjects, particularly those with ischemic electrocardiographic changes and chest pain during stress, may have ischemic heart disease not depicted by coronary arteriography.

The results of this investigation support the contention of Mason and Likar[14] that multiple lead electrocardiography increases the diagnostic yield of exercise electrocardiography, since a number of significant ST-segment changes occurred only in the limb leads (i.e., II, III, AVF).

Hypoxemia testing was done without incident in over 100 subjects in this study. While oximetry was utilized to follow the arterial oxygen saturation, this is probably unnecessary when the test is employed only in patients without significant arterial oxygen desaturation at rest. It is the authors' belief that continuous monitoring and display of the ECG is by far more important during hypoxemia as well as exercise.

Summary

Exercise and hypoxemia electrocardiography were done when the resting ECG was normal in 35 normal control subjects, in 25 with atypical chest pain not believed clinically to be angina pectoris, and in 43 patients with typical angina pectoris. Coronary arteriography was done in all 68 patients of the latter two groups. Two of the patients believed clinically to have no coronary disease had minimal angiographic evidence of arteriosclerosis. Six of the patients with typical symptoms of angina pectoris had normal coronary arteriography.

In both the normal controls and those with angiographically normal vessels about 10 per cent had ischemic ST depression (segment flat for $\geq$ 0.08 second) $\geq$ 0.5 mm with hypoxemia. Depression of the R-ST junction alone was seen in the 3[?] patients with coronary disease hypoxemia produced ischemic ST depression $\geq$ 0.5 mm in 67 per cent, J depression in 7 per cent, and no ST change in 26 per cent.

The in-exercise ECG showed J depression averaging 1.0 mm in 83 per cent of the controls and in 48 per cent of the angiographically normal patients. Ischemic ST depression $\geq$ 1.0 mm occurred in only 5 per cent. In the 39 patients with coronary disease exercise produced segmental ST depression < 1.0 mm in 8 per cent, ischemic depression $\geq$ 1.0 mm in 46 per cent, J depression in 36 per cent, and no ST change in 10 per cent.

The QX, QT and QT ratios were abnormal in the majority of cases with coronary artery disease, but also in half of the normals, and were unreliable in the evaluation of ST depression.

This study has shown the relatively high incidence of J depression with exercise in both normal subjects and those with coronary disease. While false-positive tests could be held to a minimum by accepting only ischemic ST depression $\geq$ 1.0 mm as the criterion of a positive test, this finding occurred with exercise in less than half of the patients with documented coronary disease. Hypoxemia testing produced ischemic ST-segment depression $\geq$ 0.5 mm in ⅔ of the patients with documented coronary disease. Although this test was less sensitive than exercise, the ST alterations which occurred were more discriminating.

REFERENCES

1. Master, A. M., and Jaffe, H. L.: The electrocardiographic changes after exercise in angina pectoris, J. Mt. Sinai Hosp. 7:629, 1941.
2. Master, A. M., and Rosenfeld, I.: The two-step exercise test brought up to date, New York State J. Med. 61:1850, 1961.
3. Rosenfeld, I., and Master, A. M.: Recording the electrocardiogram during the performance of the Master two-step test. II. Circulation 29:212, 1964.
4. Master, A. M., and Rosenfeld, I.: Monitored and post-exercise two-step test, J. A. M. A. 190:494, 1964.
5. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The anoxemia test in the diagnosis of coronary insufficiency, Am. Heart J. 21:634, 1941.
6. Lepeschkin, E., and Surawicz, B.: Characteristic of true-positive and false-positive results of electrocardiographic 3

exercise test, New England J Med. 258:511 1958
7 Wood P McGregor M M gidson, O and Whittaker W The effort test in angina pectoris, Brit Heart J 12:363 1950.
8 R bb C P Marks, H H and M ttingly T W Value of double tandard two-step exercise test in detection of coronary disease linical and st tistical follow-up tudy of mil tary personnel and insurance applicants, T A Lif Insurance M Directors of America 40:52, 1957
9 Robb G P and Marks, H H Latent coronary artery disease. Determination of its presence and severity by the exercise lectrocardiogram, Am J Cardiol 13:603 1964.
10. Roman, L., nd Bellet, S. Significance of the QX/QT ratio nd the QT ratio (QT) in the exercise electrocardiogram, Circulation 32:435 1965
11 Bellet, S., and Muller O F : The lectrocardiogram during exercise. Its value in the diagnosis of angina pectoris, Circulation 32:477 1965.
12. Sheffield L. T Holt J H and Reeves, T J : Exercise graded by heart rate in electrocardiographic testing for angina pectoris, Circulation 32:622, 1965
13 Mason R. E., and Likar I A new system of multiple-lead electrocardiography Am. Heart J 71 196, 1966.
14 Stewart, H J and Carr H. A. The anoxemia test, Am. Heart J 48:193, 1954
15 Judkins, M P Selective coronary arteriography a percutaneous transfemoral technic, Radiology 89:815, 1967
16. Robinson S. Experimental studies of physical fitness, Arbeitsphysiol. 10:251 1938.

Failure of safflower oil hyperlipemia to inhibit limitation of the size of experimental streptokinase-treated myocardial infarction

Dieter Burckhardt M D
Cesar A Vera M D
John S LaDue M D Ph D
New York N Y

Previous studies have shown that saturated fat accelerates the clotting mechanism and inhibits fibrinolysis. Several authors have described the inhibitory effect of alimentary lipemia upon fibrinolysis.[1-3] Bang[4] suggested that fibrin strands tend to aggregate and form clusters around the fat globules. Such structural aberrations in fibrin polymers formed in lipemic plasma may in part account for the resistance of lipemic clots to fibrinolysis.

Connor and associates[5] found a progressive shortening of the thrombus formation time as the chain length of the fatty acid increased. This change in clotting mechanism was probably due to activation of the Hageman factor. The highly unsaturated fatty acids had no effect upon thrombus formation. Evidence for the clot promoting effect of long-chain fatty acids by activation of factor XI was given by Botti and Ratnoff. Other investigators described the inhibition of plasmin by β-lipoprotein, the inhibitory effect being proportional to the concentration of the latter. Kerr and associates showed that various phospholipid fatty acid solutions were able to cause platelet aggregation in vitro, probably due to release of platelet adenosine diphosphate.

Our laboratory has[9] described the deleterious effect of saturated fat feedings upon fibrinolytic salvage of experimental myocardial infarction. We found a significant difference in the gross size of infarction and the micropathology in animals pre-fed cream compared to fasted dogs. This difference was seen in all groups of fat-fed animals regardless of the level of circulating fibrinolytic activity (FA) or serum fibrinogen, which would suggest an inhibiting effect of fat at the tissue level.

The purpose of this study was to investigate whether hyperlipemia due to unsaturated fat inhibited the salvage of myocardium induced by administration of streptokinase, the protocol being the same as in the saturated fat experiments.[9,10]

Material and methods

A total of 20 mongrel dogs were starved for three days except for water ad libitum. On the morning of the experiment

From the Department of Medicine, Memorial Hospital and Division of Clinical Investigation, Sloan-Kettering Institute, Cornell University Medical School, New York, N Y
This investigation was supported by Public Health Service research grant HE-0 from the National Heart Institute and United States Public Health Service grant CA-08748.
Received for publication July 1967

they were fed 400 c.c. of safflower oil* by gastric tube. Two hours later the animals were anesthetized with intravenous pentobarbital and respiration was maintained with ambient air through a respirator. Thoracotomy was performed by aseptic technique and the left anterior descending branch of the coronary artery was clamped below its first side branch by a method previously described.[11] A nylon string was tied to the clamp and passed through a distant intercostal space through the chest wall. The chest wall was then closed. After three hours, the string was pulled so as to remove the clamp from the coronary vessel. In all animals specimens of blood were tested for FA, fibrinogen, prothrombin time, and turbidity before the feeding of unsaturated fat, three hours after removal of the clamp, and then twice daily for four days. The animals were divided into control and treated groups.

Two hours after coronary occlusion the *treated group* of ten dogs was given an infusion of 5 per cent dextrose in water with streptokinase over a period of five hours. The amount of streptokinase was determined by a dose-prediction test modified after Lee and White[12] and varied from 33,600 to 232,000 units per hour. In four dogs thrombelastograms were performed before and after the infusion of streptokinase.

The *control group*, consisting of ten animals, was managed the same way but without the addition of streptokinase to the infusion.

All dogs were autopsied on the seventh day. Five minutes before the terminal injection of 650 mg. of intravenous pentobarbital, 5,000 U.S.P. units of heparin were given intravenously. In all animals included in the study the clamp was free of the coronary artery.

The heart was then removed and transsected serially from the base to the apex at intervals of 1 cm., starting below the site of the previous coronary occlusion. The areas of infarction were measured and sketched in each transsection as accurately as possible (see Fig. 6). Histologic sections were obtained from the central and marginal zones of the infarcted area and from the normal posterior wall of the left ventricle.

Fibrinolytic activity (FA). To 1 ml. of oxalated dog plasma, kept on ice, 0.05 ml. of thrombin solution* and 0.1 ml. of a 0.1M phosphate buffer (pH 7.6) containing 0 to 2,000 units of streptokinase† were added. The mixture was placed immediately in a 37° C. water bath and the time of lysis observed by tilting the test tube in the bath every 5 seconds. The time for complete lysis was recorded and defined as the fibrinolysis time. By varying the amount of streptokinase from 0 to 2,000 units a lysis time in the range of 0 to 60 minutes was obtained.

We defined FA as the reciprocal of fibrinolysis time in seconds times units of streptokinase used multiplied by a constant factor of 10,000.

$$FA = \frac{1}{\text{Fibrinolysis time (in seconds)} \times \text{amount of streptokinase (in units)}} \times 10{,}000$$

A prolongation in fibrinolysis time represents therefore a fall in FA and vice versa.

Fibrinogen was determined by the method described by Sharp.[13] *Prothrombin time* was determined by the Quick method[14] and *serum turbidity* by a modification of the method of Kunkel and associates.[15]

Dose prediction test. To 0.5 ml. of oxalated dog plasma 0.1 ml. of streptokinase solution containing 14 to 250 units, and 0.1 ml. of 25 units of thrombin solution were added and the mixture was placed in a 37° C. water bath. The amount of streptokinase (SK) used to obtain a complete lysis within 25 to 30 minutes was then multiplied two times by the estimated plasma volume in milliliters. This dosage of SK was infused hourly for five hours. SK dosage per hour = units SK × 2 × estimated plasma volume in milliliters.

*Saff-o-life, General Mills, Minneapolis; iodine number 145.

*Thrombin, Parke Davis Company, Detroit, Mich. [illegible] [illegible], 0.05 c.c. containing 25 units of thrombin.

†Streptokinase C.J. 20,000 units per vial, containing less than 700 units of streptodornase, lot 717928, Lederle Laboratories, Pearl River, N.Y.

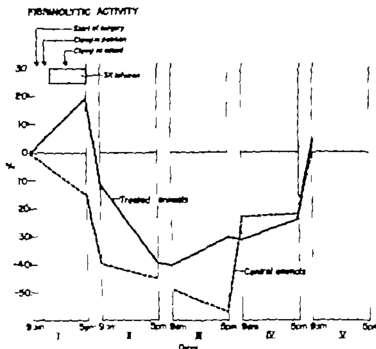


Fig. 1 Compares the average percental change in FA of the treated and control animals. The difference between control and treated dogs was not significant (P > 0.05).

Results

Fibrinolytic activity (*FA*). In all dogs (treated and untreated) the FA was not altered by the administration of safflower oil.* The untreated animals after temporary occlusion of the coronary artery had a progressive fall in FA which reached its lowest measured value 52 hours after coronary occlusion.

In the treated animals the FA showed a minor rise after infusion of streptokinase but fell subsequently in a similar fashion as in the control or untreated group. No statistically significant difference between the two groups was obtained by the Student t test (P > 0.05) because of marked variation in FA from dog to dog (Fig. 1). The administration of the predicted streptokinase dosages therefore did not result in a significant measurable increase in circulating FA.

Fibrinogen. Fibrinogen levels were not altered in either the treated or untreated groups by administration of safflower oil. After temporary occlusion of the coronary artery there was a progressive rise in fibrinogen in the untreated dogs which reached its maximum 52 hours after coronary occlusion.

After infusion of streptokinase a minor drop in fibrinogen was recorded in the treated group which was followed by a temporary rise similar to that observed in the control group. Because of great variations in fibrinogen levels from dog to dog the difference between the two groups was not significant (P > 0.05) (Fig. 2). The secondary rise in fibrinogen in both groups was probably due to the myocardial infarction itself or the operation.

Prothrombin time. Prothrombin time was not significantly altered throughout the experiment in both groups. No significant difference was found between the control and treated animals (P > 0.05) (Fig. 3).

*Since no change in FA after administration of safflower oil was observed in any of 20 dogs, the first two samples were averaged in each dog and the changes in FA, occurring in the following blood specimens, expressed in per cent.

*Since no change in fibrinogen after administration of safflower oil was observed in any of 20 dogs, the first two blood samples were averaged in each dog and the changes in fibrinogen, occurring in the following blood specimens, expressed in per cent.

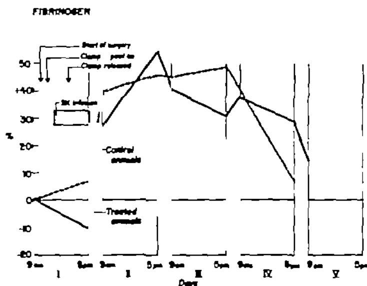


Fig. 2. Compares the average percental change in fibrinogen of the treated and control animals. The difference between control and treated dogs was not significant ($P > 0.05$).

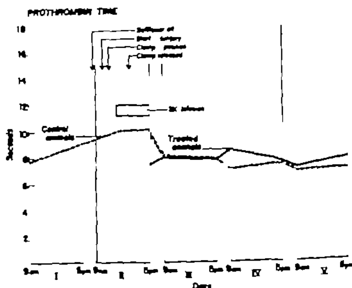


Fig. 3. Depicts the average change in prothrombin time occurring in the treated and untreated group over a five-day period. No significant difference between the two groups was found ($P > 0.05$).

Serum turbidity (ST). ST was low in both groups after the three-day starvation period. Following the administration of 400 c.c. of safflower oil, the ST rose and subsequently fell in a similar fashion in both groups. Although ST does not quantitate the exact degree of hyperlipemia, it does indicate that the safflower oil was absorbed from the gastrointestinal tract. The change in ST over the following three days was not significantly different in the two groups ($P > 0.05$) (Fig. 4).

Thrombelastogram. In four treated dogs, thrombelastograms were performed which showed a decrease in maximum amplitude as well as some increase in reaction and clotting time after the infusion of streptokinase (Fig. 5).

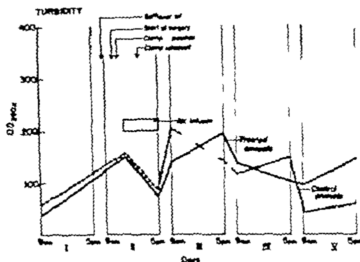


Fig. 4 Demonstrates the average change in serum turbidity of the treated and the untreated dogs over a five-day period. The initial rise in serum turbidity after safflower oil feeding was significant both groups (P < 0.01) but no significa t difference between the tw groups was found (P > 0.05)

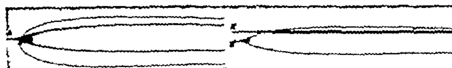


Fig. 5 Shows the thrombelastograms of t dogs before and after streptokinase infusion Maximum amplitude is markedly decreased and reaction and lotting time scores hat increased after treatment. The thrombelastograms ere similar in two other dogs tested.

Gross extent of myocardial nfarction (macroscopic findings) In Fig 6 all ten untreated dogs developed transmural in farcts.

In the treated group only one of ten animals showed a t ansmural infarct the infarctions in four dogs were rather small and subendocardial and were spotty in four other dogs. In one animal no macroscopic evidence of myocardial infarction could be found.

Microscopic find ng The microscopic findings in the ten treated and ten control dogs are listed in Table I

Discussion

We have previously shown n our labora tory that fibrinolyt c therapy after ex perimental myocardial infarction in fasting dogs markedly limits the size of infarcts and the incidence of microthrombi fibr n thrombi and interstitial edema. In similar studies in dogs pre fed saturated fat intense fibrinolysis had no effect on the gross or microscopic findings at autopsy

Instead of heavy cream the 20 dogs in our study were g ver 400 c.c of unsatu rated safflower oil prior to production of acute experimental myocardial infarction An equal resorption of the oil by both treated and control group was documented by a similar rise n ST after an initial three-day starvation period Although no significant differences were observed n the circulating FA between control and streptokinase treated animals the marked decrease in the infarct size in the treated dogs can best be explained by increased clot lysis within the microcirculation of the developing infarct. The fact that no significant differences were observed be tween the treated and control series in the circulating FA fibrinogen levels or prothrombin time emphasizes that the

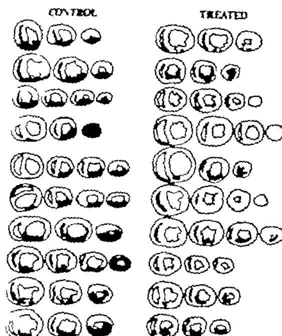


Fig. 6. Shows the striking decrease in the size of infarctions in streptokinase-treated animals.

Table I. The microscopic findings in the ten treated and ten control dogs

Microscopic finding	*Streptokinase-treated animals*	*Control animals*
Fibrinous pericarditis	3	8
Myocardial changes		
Fibrosis	5	10
Granulation tissue	5	6
Cell infiltration	7	9
Interstitial edema	6	10
Hemorrhages	4	7
Fibrin deposition (interstitial)	3	10
Microthrombi	0	0

decreased size of myocardial infarcts was not dependent upon gross measurable changes in these modalities.

As shown in Fig. 6 only one out of ten treated animals developed a transmural infarct compared to all ten dogs in the control group. The incidence of fibrinous pericarditis, myocardial fibrosis, interstitial edema, hemorrhage, and fibrin deposition was less frequent in the treated animals. Therefore, hyperlipemia due to safflower oil in contrast to heavy cream did not inhibit the salvage of myocardium by streptokinase treatment. The mechanism of inhibition of infarct size by streptokinase after saturated but not after unsaturated fat feedings is not clear. Inhibition of thrombus formation at the periphery of infarction by streptokinase seems most probable to the authors. Early clot lysis in the greater coronary vessels after removal of the clamp may be another explanation.

Microthrombi were absent in both the treated and the control group (Table I). The absence of microthrombi in dogs fed unsaturated fats as compared to their presence in previously studied groups given saturated fats[16] is worthy of emphasis. The size of infarcts in control animals fed saturated fat with widespread microthrombi was slightly greater than in control dogs fed unsaturated fat. It is possible that hyperlipemia due to saturated fat inhibits normal fibrinolysis of the vascular thrombi whereas hyperlipemia due to unsaturated fats may not. Whether this evidence of the danger of saturated fat hyperlipemia in dogs will be applicable in humans requires further study.

Summary

A total of 20 dogs were given 400 c.c. of high unsaturated safflower oil three hours before experimental production of acute myocardial infarction. Ten were given streptokinase and ten were not treated. Autopsy findings were highly significant since only one of the ten treated dogs developed a transmural infarct, whereas all of the ten untreated or control dogs showed large transmural infarctions. The infarcts in the treated animals were small, spotty, nonconfluent, and frequently subendocardial.

The fact that the protective effect of streptokinase occurred in nine dogs without significant change in circulating FA suggests that therapeutic thrombolysis occurred at the tissue level by activation of fibrinolysin contained in the clots in the coronary circulation.

These findings suggest that hyperlipemia due to unsaturated fat does not inhibit FA at the tissue level.

Striking was the absence of microthrombi

in all dogs, treated or untreated whose hyperlipemia was due to safflower oil in contrast to the microthromboses seen in animals (treated or untreated) with saturated hyperlipemia.[19]

We are indebted to Dr Isabel Mountain for the statistical analysis and to Miss Astra Parts and M Alberto Da Silva for technical assistance.

REFERENCES

1 Greig, H. B. W and Runde, I A. Studies on the inhibition of fibrinolysis by lipids, Lancet 2:461 1954
2 Bang, N L and Clifton E E. The effect of alimentary hyperlipemia and thrombolysis in vivo, Thromb. et Diath. Haemorrh. 4 149 1960.
3 Bang N L Studies by the electron-microscope, Thromb. et Diath. Haemorrh (Suppl. 1) 6:262, 1960.
4 Connor W E., Hoak, J C., and Warner E. D The effect of fatty acids on blood coagulation and thrombosis, Thromb. et Diath. Haemorrh. 17:89 1965.
5 Botti, R. E., and Ratnoff O. D The clot promoting effect of soap and long-chain saturated fatty acids, J Clin. Invest 42:860 1963.
6 Skrzydlewski, Z., Niewiarowski, S., and Skrzydlewska, J Inhibition of proteolytic enzyme by β-lipoprotein, J Atheroscler Res. 6:273 1966.
7 Kerr J W Pirrie, R. McAuley I and Bronte-Stewart, B. Platelet-aggregation by phospholipids and free fatty acids, Lancet 1:1296, 1965.
8 Haslam R. J Role of adenosine diphosphate in the aggregation of human blood-platelets by thrombin and by fatty acids, Nature 202 765 1964.
9 Sydick, I Ruegsegger P Streuli, F., and LaDue, J S Physiologic bases for thrombolytic therapy of acute myocardial infarction, Sterling, N E., editor Anticoagulant therapy in ischemic heart disease, New York, 1965, Grune & Stratton, Inc., pp. 97 110.
10 LaDue, J S., Sydick, I Streuli, F Hutter R N P and Ruegsegger P Deleterious effect of acute fat feedings upon fibrinolytic salvage of myocardial infarction, Abstracts of the IV World Congress of Cardiology Oct. 7 to 13, 1962, Mexico City p. 205
11 Sydick, I Ruegsegger P Bourier C., Hutter R. N P Abarques, R Clifton, E. E., and LaDue, J S. Salvage of heart muscle by fibrinolytic therapy after experimental coronary occlusion, Am. Heart J 61:93, 1961
12 Lee, R L, and White, P D A clinical study of the coagulation time of blood, Am. J M. Sc. 145:495 1913
13 Sharp, A. A. Viscous metamorphosis of blood platelets a study of the relationship to coagulation factors and fibrin formation, Brit. J Haemat 4:28, 1958
14 Quick, A. J and Stefanini, M The state of component A (prothrombin) in human blood, J Lab. & Clin. Med. 34:1203, 1949
15 Kunkel, H. G., Ahrens, E H and Eisenmenger W J Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease, Gastroenterology 11:499 1948.

Regional differences in magnesium, calcium, and zinc composition of arterial wall in normal and hypertensive dogs

Grace M. Fischer, M.D.
Ela I. Muta, Pharm.D.
*Josep G. Llaurado, M.D.**
Philadelphia, Pa.

It is well recognized that different regional arterial beds exhibit different basal tone or resting resistance. It is also known that arterial wall specimens from different parts of the vascular tree may respond differently in vitro to the same pressor agent.[1-4] Although regional variation in function of arteries has thus been found, little has been done to characterize variations in structure of arterial wall among the different beds and to see whether some correlation between function and structural composition may exist. Since the structural components of vessel wall, including smooth muscle, connective tissue and electrolytes, affect resistance and contractility by contributing to the viscous and elastic properties of the wall,[5] a systematic analysis of these components would seem a logical first step in an attempt to explain variations in contractility among beds. A knowledge of structure may furnish some insight as to why some beds are more active than others in regulating blood flow and pressure.

The arterial connective tissue composition has been shown to vary in different parts of the arterial tree, and its contribution to regional distensibility has been discussed. By inference the amount of smooth muscle varies also. Jones and associates[7] have reported on the variation in sodium, potassium, chloride, and water content in various parts of the arterial tree.

Apart from regional variation in electrolyte composition of arterial wall, attempts have been made to demonstrate differences in content between normal and hypertensive vessels, the rationale being that changes in wall electrolyte content will affect the stiffness and contractility of the wall. Peterson[8] has reviewed the findings of a number of investigators as to sodium (Na) and potassium (K) content. In general Na and water have been found to increase in hypertension, but K and chloride (Cl) have been variable. Tobian and Chesley have indicated that calcium (Ca) content of rat mesenteric arterioles is increased in renal hypertensive rats.

The present report is concerned with variation in arterial wall content of three

From Bockus Research Institute of University of Pennsylvania, 19th and Lombard Streets, Philadelphia, Pa. 19146.
Supported by Research Grants United States Public Health Service HE 07762 and N-ONR 551 (54) and by Special Fellowship (GMF) United States Public Health Service 7 F-3 HE-19 481-01A.
Received for publication July 13, 1967.
*Address: Neuroscience Research Laboratories, Marquette University and Veterans Administration Hospital, Wood, Wis. 53193.

divalent cations magnesium calcium and zinc. The first part of the report describes regional variation and the second part of the report compares normal with hypertensive values in dogs. Determinations of these elements in biological tissues have hitherto been difficult or tedious. Atomic absorption spectrophotometry has introduced rapidity accuracy simplicity and sample economy into the estimation of many metal elements in biological materials, thus facilitating their analysis.

Methods

Ten normal mongrel dogs of either sex were killed instantaneously by means of a Schermer mechanical stunning apparatus. Arterial specimens of about 60 mg were dissected immediately from the following sites ascending aorta (1 5 cm above valves) descending aorta (1 cm below left subclavian) thoracic aorta (2.5 cm. above diaphragm) abdominal aorta (between cranial mesenteric and renal) proximal cranial mesenteric distal cranial mesenteric, small branches of cranial mesenteric renal femoral (from region of femoral triangle) popliteal pulmonary (0 5 cm above valves) and carotid (adjacent to lower part of thyroid cartilage) Dissections were completed rapidly to prevent postmortem changes from occurring The specimens were cleaned weighed dried and defatted as previously described and were then weighed and stored until time of analysis. For analysis the specimens were ashed over a period of 18 hours at 500° C in silica crucibles. Each ashed specimen was dissolved in 1 ml of concentrated hydrochloric acid (HCl) and diluted with lanthanum solution and distilled water so that the final concentration of lanthanum was 1 per cent, the lanthanum offering protection against interference by phosphorus Calcium and zinc were determined directly on this solution. For magnesium a 1 6 dilution was made with 1 per cent lanthanum to bring the concentration to a level which resulted in the proper absorption range It should be noted that strong concentrations of HCl will affect the absorption of calcium and zinc and to slight extent magnesium so that it is important to prepare standards of the same acid normality as the specimens. A model 303 Perkin Elmer atomic absorption spectrophotometer with suitable emission lamps was used for all determinations.

For the hypertensive series, nine female mongrel dogs were made hypertensive by the kidney cellophane wrapping method. Blood pressures, measured intrafemorally before kidney wrapping ranged from 120/74 to 180 95 and in the late hypertensive phase from 164/106 to 310 155 The development of hypertension was followed in each dog individually by serial blood pressure measurements. The dogs were allowed to remain hypertensive for an average of six weeks before they were killed either by use of the Schermer apparatus or I v pentobarbital administration. No difference was observed in electrolyte values attributable to the manner of death Specimens were collected from the same sites as in the normal group with the exception that mesenteric branches and distal mesenteric specimens were obtained from only four of the hypertensive dogs All samples were processed and analyzed in the same manner as those of normal dogs.

Results

Regional differences in normal arteries Results for both normal and hypertensive dogs are summarized in Table I

MAGNESIUM IN NORMAL ARTERIES. The most striking finding as to regional variation in magnesium (Mg) content of arteries is the high set of values found for the pulmonary and all segments of the mesenteric arteries The pulmonary has a content that is significantly (t test) higher than any of the other beds with the exception of the mesenteric segments. The significance of the difference is very marked ($P < 0.0005$) between the pulmonary and mesenteric segments on the one hand and femoral popliteal carotid and abdominal aorta on the other hand Another interesting finding is the fact that the Mg content decreased in the aorta peripherad from the ascending to the abdominal ($P < 0.005$ between ascending and abdominal)

The lowest Mg content was found in the femoral artery and was also low in the popliteal carotid and abdominal. Middle range values were found for the ascending

Table I. Concentration of magnesium calcium and zinc in arteries from normal and hypertensive dogs milliequivalents per kilogram of dry defatted tissue (mean ± S. E.) and per cent of nonconnective tissue elements

Artery	Magnesium		Calcium		Zinc		Nonconnective tissue elements (% of dry defatted weight)	
	Normal	Hypertensive	Normal	Hypertensive	Normal	Hypertensive	Normal*	Hypertensive†
Aorta, ascending	25 1	7 2 ± 0 8	24 9 ± 1 3	23 3 ± 1 1	3 35 ± 0 21	3 39 ± 0 28	39 8	43 3
Carotid	23 7 0	22 2 ± 0 9	21 8 ± 1 4	9 3 ± 2	4 15 ± 0 40	3 48 ± 0 33	29 2	32 2
Aorta, descending	26 3	27 8 ± 1 4	25 9 ± 2 3	23 0 ± 0 6	3 00 ± 0 17	3 63 ± 0 31	‡	42 4
Aorta, thoracic	2 ± 3	25 ± 1 1	25 9 ± 1 2	21 7 ± 0 6	3 42 ± 0 25	3 39 ± 0 20	‡	42 7
Aorta abdominal	21 2 ± 0 8	23 9 ± 0 8	26 5 ± 2 0	25 8 ± 1 0	3 38 ± 0 32	2 96 ± 0 33	21 4	23 9
Cranial mesenteric proximal	30 3 ± 0 8	28 6 ± 1 4	24 3 ± 1 5	24 0 ± 1 0	5 31 ± 0 49	3 99 ± 0 27	35 4	43 5
Cranial mesenteric distal	29 7 ± 1 0	30 4 ± 1 2	21 3 ± 2 9	22 ± 1 4	4 42 ± 0 61	4 71 ± 0 40	40 3	47 7
Cranial mesenteric branches	31 ± 0 7	30 6 ± 1 2	22 7 ± 1 5	23 3 ± 3 3	4 87 ± 0 43	87 ± 0 51	42 1	43 8
Renal	37 3 ± 1	27 7 ± 1 3	32 3 ± 4 4	21 5 ± 1 2	4 14 ± 0 20	4 19 ± 0 33	35 7	41 4
Femoral	5 ± 1	19 0 ± 0 6	21 ± 1	20 8 ± 1 0	2 95 ± 0 32	96 ± 0 13	51 0	3 7
Popliteal	2 4 ± 8	23 0 ± 0	21 7 ± 7	20 ± 1 6	3 98 ± 0 39	4 00 ± 0 31	‡	29 5
Pulmonary	31 7 ± 1 2	30 0 ± 0 9	27 3 ± 1 8	21 8 ± 0 9	4 03 ± 21	3 32 ± 39	‡	44 3

*Derived from results published in reference
†Derived from results published in reference 22
‡Observations not available for this location

descending thoracic aorta and renal artery

CALCIUM IN NORMAL ARTERIES In general the regional variation of Ca content was not as marked as that of Mg The renal artery had the highest content, but this artery also showed more variation as can be seen from its standard error This was due to the occurrence of unusually high values for several of the normal renal arteries. This finding is unexplained. There were no gross calcified plaques apparent in the vessels. The pulmonary had a relatively high concentration of Ca. In general higher values for Ca were found in the great vessels than in the small vessels. In most cases the difference was statistically significant for instance pulmonary thoracic aorta, and abdominal aorta on the one hand vs. carotid femoral and popliteal on the other hand There was a tendency for the Ca content to increase peripherad in the aorta but the difference between the ascending and abdominal aorta contents was not significant.

ZINC IN NORMAL ARTERIES The highest values for zinc were found in the mesenteric vessels. The lowest value was found in the femoral artery The differences were statistically significant between the femoral and all segments of the mesenteric ($P < 0.0005$ for proximal, $P < 0.025$ for distal $P < 0.005$ for branches) Except for the high mesenteric content and low femoral content, the zinc (Zn) did not parallel the Mg levels among the different sites The differences among sites were not so marked as they were for Mg and could not be correlated with size, as for Ca.

Regional differences in hypertensive arteries It can be seen that the site variation in hypertensive arteries paralleled the site variation in normal arteries. The Ca content of the renal artery was lower in the hypertensive group, but this might be attributed to the unexplainable high value found in the normal group.

Normal versus hypertensive arteries In no case was the Mg content of a hypertensive vessel significantly different from that of the same site vessel in the normal state

As to Ca content in only three vessels was the difference significant and in each case the hypertensive value was *lower*

than the normal value renal ($P < 0.025$) thoracic aorta ($P < 0.005$) and pulmonary ($P < 0.01$)

In only one vessel the proximal mesenteric, was the Zn content significantly different ($P < 0.025$) in the hypertensive state being lower than in the normal.

Thus, in general the state of renal hypertension had little effect upon total arterial wall content of Mg Ca and Zn

Discussion

There is a paucity of data in the literature concerning the Ca content of arteries. Most studies have been limited to the aorta and have been oriented to the study of atheroma formation Wallach and associates[11] reported control values of Ca in dog aorta to be 24.4 ± 2.0 mEq per kilogram of dry fat free weight (DFFW) tissue.

Magnesium data for arteries are also scarce and scattered Wallach and associates[11] reported Mg values for dog aorta of 31.3 ± 1.3 mEq per kilogram of DFFW tissue Burch and co-workers[12] reported values for canine aorta of 23.5 mEq per kilogram and for canine pulmonary artery of 26.4 mEq per kilogram of dried sample Somlyo and associates[13] reported values for canine iliac arteries of 26.6 mEq per kilogram of dry tissue. All are in the same range as our results

The Zn content of aorta has been reported to be 32 ppm of fresh tissue, which would be roughly equivalent to 3.33 mEq per kilogram of DFFW tissue Tipton[14] has reported a median value for Zn in human aorta of 1.950 µg per gram of ash which is approximately equivalent using his conversion factors, to 2.44 mEq per kilogram of DFFW tissue

The contribution of electrolytes to arterial wall properties and function has been the subject of investigation along several lines of approach Bohr[15] has reviewed extensively the relationship between electrolytes and smooth muscle contraction. Briefly as to divalent ions calcium is known to have a dual action on smooth muscle contraction depressing membrane excitability but augmenting the coupling of membrane excitation with the development of tension by the contractile protein its greater effect being to enhance smooth muscle contraction. The major effect of Mg is to decrease the magnitude of smooth muscle contraction.

Zn has been found to be a constituent of certain enzyme systems such as pyridine nucleotide-dependent dehydrogenases (muscle lactic dehydrogenase) Zn content has been found to be higher in red muscles than in white muscles in the pig red muscles having a more continuously active or tonic function than white ones.[3] Zn has been found to prolong the excited state of skeletal muscle in vitro[16] but to depress cardiac muscle.[17]

Regional variation in magnesium content The fact that Mg is largely an intracellular ion would lead one to consider whether high Mg content would be found in arteries with high smooth muscle mass. Jones and associates found the highest K content to be in the pulmonary artery Since K is also an intracellular ion high Mg and K in the pulmonary artery might indicate a large cellular mass, i.e. large smooth muscle mass. This correlation was investigated by estimating smooth muscle mass in arterial wall from data on connective tissue composition of arterial wall in normal and hypertensive[18] dogs If noncon nective tissue mass is considered largely to represent smooth muscle mass, the regional variation in smooth muscle mass can be obtained from these data. Table I includes per cent composition of noncon nective tissue elements in arterial wall. Comparing these values site by site to the values for Mg one can see that the general trend is toward a high smooth muscle mass being associated with a high Mg content. The pulmonary and mesenteric arteries are most marked in this respect in that they would have high content of both smooth muscle and Mg whereas the femoral would have low content of both.

Our results indicate a decreasing Mg content peripherad along the aorta from the ascending to the abdominal. This trend can be seen in the smooth muscle also.

Thus Mg content would seem to be correlated with smooth muscle mass. Whether this is due passively to the cellular nature of the tissue or whether the high Mg assumes significance in an active role in the contractile process would require further investigation.

Regional variation of calcium and zinc Ca content did not vary in the same manner as Mg Size of vessel appears to be a factor in calcium content since large vessels tend to have a higher concentration than small vessels. There was no evidence of plaque formation in the vessels analyzed although microscopic deposition of Ca in the walls may not be ruled out. There is indication that mucopolysaccharide content of aorta is higher than that of peripheral vessels[23] thus a high Ca content in great vessels might possibly be related to binding of Ca to connective tissue mucopolysaccharides

The high Zn concentration in the mesenteric vessels perhaps could bear some relationship to the amount of smooth muscle and therefore enzyme activity during contraction The fact that the mesenteric a very labile bed and probably very active when not in the resting state would be consistent with high Zn values.

Hypertensive vs normal The roles of Mg Ca and Zn in the hypertensive process are at present obscure Tobian and Binion[5] have analyzed autopsy specimens of renal artery from normotensive and hypertensive patients and have found no difference in Mg content. Tobian and Chesley[6] have reported an increase in Ca content in rat mesenteric arterioles of hypertensive animals. In their comparison however their control animals were not strictly normal but rats which had been made hypertensive and then returned to normal There are conflicting reports concerning increase or decrease of serum Ca or Mg in the hypertensive state in humans. Frohlich[24] has reported plasma concentrations of Ca falling and of Mg rising as renal involvement became more manifest with progression of disease. Albert and associates[14] have found serum Mg concentration decreased in hypertensive patients. Bauer and co-workers[27] reported that exchangeable body Mg expressed per kilogram of body weight, was decreased in hypertensive men but not in hypertensive women. Seller and associates[28] have discussed Mg in reference to hypertension and have suggested that changes in Mg metabolism influence vascular tone and play an integral role in blood pressure control Schroeder and Perry[29] have discussed the antihypertensive effects of metal binding agents. Schroeder[30] has found an elevated ratio of cadmium to Zn in urine in human hypertensive disease.

In our studies, the state of renal hypertension showed little effect on the Mg Ca and Zn concentration of arterial wall There was some tendency for Ca concentration to be reduced in hypertensive vessels but since this was significant in only three sites, caution should as yet be exercised in attributing much significance to this tendency The finding that Ca was not increased appears more important to us, from the point of view that this finding disfavors an increase in Ca augmented smooth muscle contraction as an etiological factor in the hypertension

It had previously been found that amounts of collagen and elastin in arterial wall were little affected by renal hypertension the total amount of connective tissue tending to be slightly less in the hypertensive state.[22] Jones and associates[7] found that Na and H_2O increase in hypertensive vessels. The fact that Na concentration increases in hypertensive arteries, whereas Mg and possibly K do not, would lead one to speculate that hypertensive changes involve the extracellular rather than the intracellular space.

In closing it should be noted that these findings are limited to one form of hypertension renal and may not necessarily be the same in other forms of hypertension

Summary

Mg Ca and Zn content were determined in arteries from 17 different sites in the arterial tree of normal and hypertensive dogs. Regional variation of Mg tended to parallel estimated content of smooth muscle being highest in the pulmonary and mesenteric vessels and lowest in the femoral Ca content on the other hand more closely paralleled size of vessel being highest in the great vessels. Zn content was high in the mesenteric and low in the femoral vessels.

The differences between normal and hypertensive vessels were not very marked In no site was the Mg content significantly different between normal and hypertensive vessels. In three sites, renal thoracic aorta and pulmonary Ca content was

significantly lower in hypertensive vessels. In one site proximal mesenteric, Zn content was significantly lower in hypertensive vessels. It thus appears that the state of renal hypertension is not associated with a general increase in Mg, Ca or Zn in the walls of the arterial tree.

REFERENCES

1 Dodd, W A., and Daniel, E. E. Vascular muscle reactivity Circulation Res 8:446, 1960.
2. Bevan, J A Sensitivity of the large blood vessels of the rabbit to l-epinephrine and l-norepinephrine, Circulation Res. 9 700, 1961
3. Bevan, J A., and Osher J V Relative sensitivity of some large blood vessels of the rabbit t sympathomimetic amines, J Pharmacol. & Exper Therap 150:370, 1965
4. Somlyo, A. V Sandberg R. L and Somlyo, A. P Pharmacologically heterogeneous smooth muscle cell distribution in blood vessels, J Pharmacol. & Exper Therap. 149 106, 1965.
5 Peterson, L. H Physical factors which influence vascular caliber and blood flow Circulation Res. (Suppl. I) 18:3 1966.
6. Fischer G M., and Llaurado, J G. Collagen and elastin content in canine arteries selected from functionally different vascular beds, Circulation Res. 19:394, 1966
7 Jones, A. W Feigl, E O., and Peterson, L. H.: W ter and electrolyte content of normal and hypertensive arteries in dogs, Circulation Res. 15:386, 1964.
8. Peterson, L. H. Systems behavior feed-back loops, and high blood pressure research, Circulation Res. 12:585 1963
9 Tobian, L and Chesley G Calcium content of arteriolar walls in normotensive and hypertensive rats, Proc. Soc Exper Biol. & Med. 121:340 1966.
10 Willis, J B The determinations of metals i blood serum by atomic absorption spectroscopy I Calcium, Spectrochim. acta 16:259 1960.
11. Wallach, S Bellavia, J V Schorr J and Reisenstein, D L Tissue distribution of electrolytes, Ca^{47} and Mg^{28} in acute hypercalcemia, Am. J Physiol. 207:533, 1964.
12. Burch, G. E., Lazzara, R K and Yen, T K. Concentration of magnesium in tissues of the dog Proc. Soc Exper Biol. & Med. 118:581 1965.
13. Somlyo, A. V Woo, C Y and Somlyo, A. P Effect of magnesium on posterior pituitary hormone action on vascular smooth muscle, Am J Physiol 210 705 1966
14. Underwood, E. J Trace elements in human and animal nutrition, New York, 1962, Academic Press, p. 159
15. Tipton, I H The distribution of trace metals in the human body *In* Seven, M. J and Johnson, L. A. editors Metal-binding in medicine, Philadelphia, 1960, J B. Lippincott Co p. 27
16. Bohr D F Electrolytes and smooth muscle contraction, Pharmacol. Rev 16:85 1964.
17 Bohr D F Vascular smooth muscle dual effect of calcium, Science 139:597 1963.
18. Fruton, J S and Simmonds, S. General biochemistry New York, 1958, John Wiley & Sons, Inc., p. 319
19 Cassens, R. G., Hoekstra, W G., Faltin, E C. and Briskey E. J Zinc content and subcellular distribution in red vs whit porcine skeletal muscle, Am J Physiol. 212:688, 1967
20 Isaacson, A., and Sandow A Effects of zinc on responses of skeletal muscle, J Gen. Physiol. 46:655 1963.
21 Nayler W G., and Anderson, J E. Effects of zinc on cardiac muscle contraction, Am. J Physiol. 209:17 1965.
22. Fischer G. M and Llaurado, J G. Connective tissue composition of canine arteries effects of renal hypertension, Arch. Path. 84:95 1967
23 Kirk, J E. Mucopolysaccharides of arterial tissue, *i* Lansing, A. I editor: The arterial wall, Baltimore, 1959 The Williams & Wilkins Company p 161.
4 Tobian, L., and Binion, J T Tissue cations and water in arterial hypertension, Circulation 5 754 1952.
25. Frohlich, E. D Plasma sodium, potassium, calcium, and magnesium concentrations in essential hypertension, Am. J M Sc. 248:419 1964.
26. Albert, D G., Morita, Y and Iseri, L. T: Serum magnesium and plasma sodium levels in essential vascular hypertension, Circulation 17 761 1958.
27 Bauer F K. Martin, H. E., and Mickey M. R. Exchangeable magnesium in hypertension, Proc. Soc. Exper Biol. & Med. 120:466, 1965.
28. Seller R. H., Ramirez Muxo, O Brest, A. N and Moyer J H. Magnesium metabolism in hypertension, J A. M A. 191:654 1965.
29 Schroeder H. A., and Perry H. M. Antihypertensive effects of metal-binding agents, J Lab. & Clin. Med. 46:416, 1955
30. Schroeder H. A. Renal cadmium and essential hypertension, J A. M A. 187:358, 1964.

Case reports

Origin of both great vessels from right ventricle with intact ventricular septum

Farzin Davachi, M.D.
James H. Moller, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

Origin of both great vessels from the right ventricle and its associated anomalies has been described by several authors.[1-7] In the majority of reported cases a ventricular septal defect has been present. Origin of both great vessels from the right ventricle with intact ventricular septum, on the other hand, is extremely rare. To our knowledge only two cases of this cardiac malformation are reported in the literature.[8,9] This communication presents the clinical and anatomic findings of a patient with this malformation and reviews the two previously reported cases.

Case report

Clinical features

A two-day-old infant was born following a normal pregnancy. Birth weight was 7 pounds 9½ ounces. At birth the infant exhibited cyanosis, a cardiac rate of 160 to 180 beats per minute, and tachypnea (100 to 120 beats per minute). The lungs were clear and no murmur was evident. The liver was palpable 4 cm. below the right costal margin. On the day following birth, a Grade II/VI systolic ejection murmur was present along the left sternal border. The second cardiac sound was accentuated and single. The peripheral pulses were of poor quality.

An electrocardiogram (ECG) revealed a QRS axis of +95° without evidence of atrial or ventricular hypertrophy (Fig. 1). A thoracic roentgenogram revealed moderate cardiomegaly and normal pulmonary vascular markings (Fig. 2).

The clinical impression was transposition of the great vessels and single ventricle. The infant followed a course of progressive cyanosis and dyspnea and died on the second day of life.

Necropsy observations

The great arteries were abnormally interrelated. The ascending aorta, which was hypoplastic (3 mm. in diameter), lay to the right of and at a posterior level to the pulmonary trunk with which it was parallel. The latter vessel was dilated, measuring 1.0 cm. in diameter. Each originated from the right ventricle (Fig. 3).

The structure of the right ventricle appeared essentially normal, with a hypertrophied wall measuring about 0.6 cm. in thickness (Fig. 4,A). The ventricular septum was intact and the pulmonary trunk arose in a normal position. A narrow tract behind the medial aspect of the parietal limb of the crista supraventricularis and anterior to the tricuspid valve led to the aortic origin (Fig. 4,B). Tricuspid valvular tissue corresponding to its anterior leaflet was continuous with the aortic valve. The coronary arteries arose from the aorta. The aortic and pulmonary valves were at the same horizontal body plane. The right ventricle measured 18 mm. in length from the base of the pulmonary valve to the apex of the chamber.

The venous connections were normal. Both atria were enlarged. The atrial septum showed a defect

From the Departments of Pediatrics and Pathology, University of Minnesota, Minneapolis, Minn., and the Department of Pathology, The Charles T. Miller Hospital, St. Paul, Minn.

Supported by Public Health Service Research Grant 5 RO1 HE-06494 and Research Training Grant 5 T1 HE 5570, from the National Heart Institute.

Received for publication June 1, 1967.

Address: Department of Pathology, The Charles T. Miller Hospital, 125 West College Avenue, St. Paul, Minn., 55102.

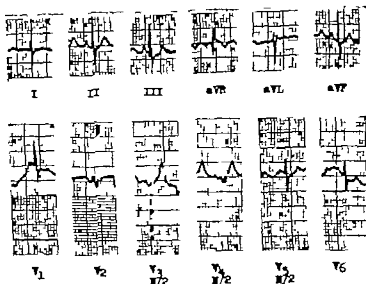


Fig. 1. The ECG. QRS axis is +95° without evidence of trial or entricular enlargement.



Fig. 2. The thoracic roentgenogram shows moderat cardiomegaly and normal pulmonary ascular markings.

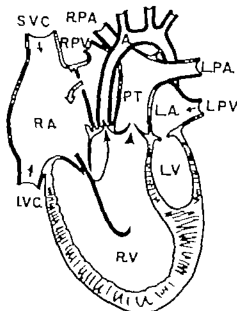


Fig. 3. Diagram showing the central circulation in case reported in which both great essels rise from the right entricle while the ventricular septum is intact.

measuring 3 by 7 mm. t the fossa ovalis on the basis of a short alv of the foramen ovale.

The left entricle was hypoplastic, the length of the left entricle from its apex t its base being 10 mm. Its all was thin measuring only 2 mm. in thickness. The mitral alv was represented by delicat leaflet-like tissue without specialized forma tion and without distinct chordal attachments (Fig. 5). No distinct papillary muscles were identifiable and the endocardium was not thickened. Except for the mitral orifice no outlet was present for the left ventricle.

Comment

When both great vessels originate from the right ventricle, it is classical that a ventricular septal defect be associated and representing the avenue of egress of blood from the left ventricle. To our knowledge, only two cases of origin of both great vessels from the right ventricle with intact ventricular septum have been reported [8,9] each case having been studied at necropsy



Fig. 4 (A) Interior of right ventricle (R.V.) and pulmonary trunk (P.T.). The relationship between this vessel and the chamber is essentially normal. Hypertrophy of right ventricular wall. Arrow indicates position leading to subaortic tract. (B) Interior of right ventricle (R.V.) and ascending aorta (A). The parietal limb of the crista supraventricularis (C.S.) has been divided and deflected toward the patient's left to reveal the subaortic tract. The latter is bounded anteriorly by the crista and posteriorly by the anterior tricuspid leaflet (T).

MacMahon and Lipa[8] described the case of a 12-week-old female infant in whom cyanosis was first noticed at six weeks of age. A pansystolic murmur was present at the fourth and fifth left intercostal spaces, and the ECG revealed right ventricular and combined atrial hypertrophy. The infant became increasingly cyanotic and died at 12 weeks of age. At necropsy both great vessels originated from the right ventricle and the ventricular septum was intact. An interatrial communication, 2 by 3 mm in dimension, was the only outlet for blood from the left side of the heart. An additional finding was left ventricular endocardial fibroelastosis extending along the linings of myocardial sinuses which communicated with the left ventricular cavity.

Ainger[9] reported the case of a two-year-old boy who developed cyanosis and congestive cardiac failure during the first six weeks of life. A continuous murmur was heard at the upper right sternal border. The infant was digitalized and at two years of age was noticed to have decreased exercise tolerance and dyspnea. An ECG showed a nearly vertical axis, a Qs pattern in Lead V_1, and small QRS complexes in Leads V_5 and V_6 without S waves. The child became more cyanotic and died 21 hours later after cardiac catheterization and angiography. Necropsy revealed origin of both great vessels from the right ventricle with an intact ventricular septum. A 5 by 6 mm atrial septal defect was present.

Previously, one of us (J. E. E.) and others[14] described a case of origin of both great vessels from the right ventricle in which a ventricular septal defect, although structurally present, was closed by adhesion of the anterior mitral valvular leaflet to the septal defect. In a 4-month-old infant the basic functional change was like that in the case herein reported. Egress of blood from the left side of the heart was accomplished by way of a small atrial septal defect, and an accessory opening in the anterior mitral valvular leaflet which permitted communication between the left atrium and right ventricle.

The condition in which both great vessels arise from the right ventricle while the ventricular septum is intact shares certain functional features with other conditions. These are mitral atresia or aortic atresia either alone or in combination with an intact ventricular septum. Usually a crucial problem in these conditions is an inadequate channel for the flow of blood from



Fig. 5. Interior of left atrium (*LA*) and left ventricle (*LV*). The tissue of the mitral valve is rudimentary. Left ventricular wall thin and chamber small. Defect (*D*) in atrial septum.

the left side of the heart. The route that this takes is through an opening in the atrial septum.

Usually this is not an atrial septal defect in the pathologic sense. Rather, an interatrial communication develops as a result of herniation of the valve of the foramen ovale into the right atrium. Elevated left atrial pressure is responsible for this herniation. Usually the interatrial communication that develops is sufficiently small as to be responsible for elevated pulmonary venous and capillary pressures.

In our case the atrial septum contained a true defect and this opening may have been sufficiently wide as to preclude a process of pulmonary venous obstruction.

On the arterial side, origin of both great vessels from the right ventricle shares with aortic and/or mitral atresia the functional phenomenon of having one ventricle (the right) supply both the lesser and the pulmonary circulations.

In aortic atresia with an intact and functional mitral valve the left ventricular wall characteristically is hypertrophied and its chamber small. The endocardium is thickened. These changes have been considered to be secondary to elevation of pressure in the trapped left ventricle. In our case, the left ventricle appeared decidedly different than the left ventricle in classical aortic valvular atresia.

We would attribute these differences to the state of the mitral valve. On the basis of its structural abnormalities, we conclude that the mitral valve was incompetent, thus preventing "trapping" of the left ventricle.

While the condition at hand shares functional features with aortic or mitral atresia, the potential for identifying the anatomic differences appears to exist in angiography.

Summary

Origin of both great vessels from the right ventricle with intact ventricular septum is extremely rare; only two cases of this cardiac malformation has been reported previously according to our knowledge.

Reported herein is the case of a two-day-old infant who exhibited cyanosis at birth and an ejection systolic murmur along the left sternal border with a normal ECG. Necropsy observation revealed origin of both great vessels arising from a dilated right ventricle with intact ventricular septum.

An atrial septal defect, hypoplasia of the mitral valve and left ventricle were present. The intracardiac hemodynamics are similar to aortic valvular atresia and/or mitral atresia with intact ventricular septum.

REFERENCES

1. Witham, A. C.: Double outlet right ventricle. A partial transposition complex, Am. Heart J. 53:928, 1957.
2. Neufeld, H. N., DuShane, J. W., Wood, E. H., Kirklin, J. W., and Edwards, J. E.: Origin of both great vessels from the right ventricle. I. Without pulmonary stenosis, Circulation 23:399, 1961.
3. Neufeld, H. N., Lucas, R. V., Jr., Lester, R. G., Adams, P., Jr., Anderson, R. C., and Edwards, J. E.: Origin of both great vessels from the right ventricle without pulmonary stenosis, Brit. Heart J. 24:393, 1962.
4. Neufeld, H. N., DuShane, J. W., and Edwards, J. E.: Origin of both great vessels from the right ventricle. II. With pulmonary stenosis, Circulation 23:603, 1961.
5. Engle, M. A., Steinberg, I., Lukas, D. S., and Goldberg, H. P.: Acyanotic ventricular septal

defect with both great vessels from the right ventricle Am Heart J 66 755 1963.

6. Levy M J DeWall, R Elliott L P and Cuello, L Origin of both great arteries from the right ventricle and pulmonary stenosis, Dis Chest 42:372 1962.
7. Witham, R A Jr Adams, P Jr Winchell, P Lester R. G Lillehei C W Edwards, J E. and Neufeld, H N Origin of both great vessels from the right ventricle without pulmonary stenosis, Am Heart J 62:415 1961
8. MacMahon, H E and Lipa, M Double-outlet right ventricle with intact interventricular septum Circulation 30:745, 1964
9. Anger L F Double-outlet right ventricle intact ventricular septum, mitral stenosis, and blind left ventricle, Am. Heart J 70:521 1965
10. Edwards, J E. James, J W and DuShane J W Congenital malformation of the heart. Origin of transposed great vessels from the right ventricle associated with atresia of the left ventricular outlet, double orifice of the mitral valve and single coronary artery Lab. Invest 1 197 1952

Propranolol in persistent ventricular fibrillation complicating acute myocardial infarction

H. Ikram, M.B., M.R.C.P., M.R.C.P.E., F.A.C.S.
London, England

Ventricular fibrillation can usually be terminated by electrical defibrillation following adequate oxygenation, efficient cardiac massage, and the correction of metabolic acidosis. In a small number, particularly those with severe cardiac damage from coronary artery disease, the arrhythmia tends to recur after minutes or hours despite meticulous attention to oxygenation and acid-base balance. In this grave situation recourse is made to antiarrhythmic drugs such as quinidine, procaine amide, and lidocaine, but successful control of the arrhythmia is infrequent.

Sloman and associates[4] reported successful control of persistent ventricular fibrillation with propranolol administered by the intravenous route. In the dosage employed by these authors the adverse effects of this drug on myocardial contractility may have become a serious problem and the authors attribute one death in their series to this factor.

The purpose of this communication is to describe the successful control of persistent ventricular fibrillation occurring in four patients with acute myocardial infarction with intravenous propranolol. The use of 1/10 the dose recommended by Sloman and associates[4] have enabled us to avoid the undesirable side effect on myocardial contractility while retaining the antiarrhythmic effect.

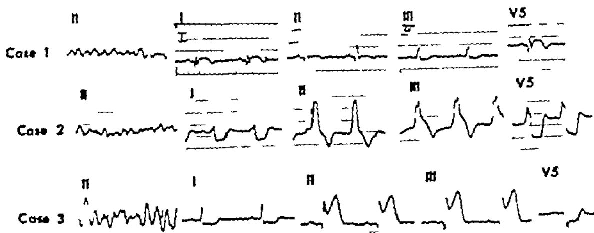
Case reports

Case 1. J. G., a 54-year-old Canadian business man was admitted to the hospital with recent cardiac infarction. The electrocardiogram (ECG) showed the pattern of a massive, fresh anterior infarction. Shortly after admission to the ward, he collapsed. Closed-chest cardiac massage and emergency ventilation were started immediately. Ventricular fibrillation was present on the ECG (Fig. 1). A direct current (D.C.) shock of 200 joules was administered. Following the shock, ventricular tachycardia developed which reverted to ventricular fibrillation within a few minutes. An infusion of 8.4 per cent $NaHCO_3$ was commenced and 100 ml. administered before defibrillation was attempted again. A shock of 300 joules was applied. The fibrillation reverted to ventricular tachycardia for a few minutes before recurring. The above sequence of events was repeated after two more shocks at 400 joules. A dose of 1 mg. of propranolol was given intravenously and a further shock applied. Following this, supraventricular tachycardia developed which was sufficient to produce a blood pressure of 100/60. The patient regained consciousness and began to object to the endotracheal tube. Intravenous morphine was given to produce an adequate level of sedation. A little later sinus rhythm occurred spontaneously. Apart from retrograde amnesia for the duration of the episode, the mental state was quite clear. The postresuscitation ECG showed the changes of an extensive acute anterior infarction. The peak serum glutamic oxalacetic transaminase (SGOT) was 272 Sigma-Frankel units.

The patient's recovery was complicated by congestive cardiac failure which responded to digitalis and diuretics. He has since returned to work in Canada.

Case 2. E. G., a 51-year-old man, collapsed in the Casualty Department. External cardiac massage and emergency ventilation were commenced immediately. An ECG showed ventricular fibrillation

From the Charing Cross Hospital, London, W. C. 2, England.
Received for publication June 1, 1967.



F J ECG Cases 1 2 nd 3 taken just before and shortl after the final D C defibrillation which resulted i able rh thm Case 2 show complet heart block which resolved ery shortly after

A of sion of 8 4 per cent sodium bicarbonate was ommenced and total of 250 ml nfused. Two D C shock of 100 nd 300 joules were applied to the best After ach shock hythm capable of producing pulse the wrist resulted but relapsed 2 int entricular fibrilla ion after few minutes. A dose of 100 mg of procaine amide was given intra enously nd tw further hocks were pplied after an interval of ten min tes The same sequence of arrhythmias was repeated 1 mg of propranolol was given tra enously and fi minutes later further D C shock was pplied This resulted in complet A V block w h entricular rat sufficient t produ blood pressure of 100/60 w thout pressor drugs The patient rapidly recovered consciousness. The ECG showed extensive acut posterior infarct. The peak SGOT w 230 Sigma-Frankel units. The patien regained sinus hythm in about half n hour after the successful defibrillation.

His recovery was complicated by congestive f ilure which responded t diuretics and digitalis. H has now been back t work for si months.

Case 3 J T 64-y ar-old man with a previous history of hronic bronchitis, was admitted t the ward w th severe cardiac pain A ECG showed massiv posterior infarction Shortly after he col lapsed. Cardiac arrest due t ventricular fibrillation was diagnosed and emergency entilation and losed hest cardiac massage was commenced I tra enous infusion of 8 4 per cent sodium bicarbonat was tarted and total of 200 ml. administered Three hocks t 200 250 and 300 joules were administered. After each shock, the entricular fibrillation reverted to supra entricular rhythm for short periods before relapsing again. A dose of 1 mg of propranolol was given intra enously and fourth shock of 400 joules was applied fi minutes later A stable supra ventricular tachycardia capable of generating a blood pressure of 90/60 resulted. I view of the complicating chronic bronchitis and emphysema, he was vent lated for 12 hours by means of Bird Mark 8 ventilator The peak level of SGOT w 300 Sigma-Fra kel n ts. His recovery was compli cated by the development of congestiv cardiac failure which responded to digitalis and diuretic therapy H is now back to an activ life, though he still requires d gitalis and diuretics

Case 4 E. H 73-year-old woman, was admitted to the hospital with the changes of massive posterior infarction The peak SGOT was 320 Sigma-Frankel units She appeared to be making satisfactory recovery when she developed further extension of her cardiac infarction. She was making slow recovery from this when a further episode of chest pain was followed by cardiac arrest in entricular fibrillation. Emergency entilation and losed-chest massage were commenced immediately An intra enous inf sion of 8 4 per cent $NaHCO_3$ w commenced and she was given 150 ml. Two shocks t 250 and 300 joules were pplied afterward I both cases, the shock resulted in ventricular tachycardia which rapidly relapsed into entricular fibrillation. A dose of 1 mg of propranolol was given intra enously and further hock of 300 joules applied. The same sequence of events recurred. After further delay of three to fou m nutes, a further shock was applied. This resulted in a table rhythm though the gross deformity of the ECG due to repeated infarctions made it difficult t diagnose the arrhythmia more precisely A blood pressure of 60/40 resulted and this was boosted t 100/60 by means of an infusion of epinephrine. The blood pressure, however gradually declined and pulmonary edema dev loped Despit all therapy the patient died 14 hours later Postmortem examination showed extensiv infarction of the left entricle with only about ⅓ of the wall nlerolved by the infarction.

Discussion

The effects of adrenaline on the irritability and contractility of the myocardium are mediated by β-adrenergic receptors. Many cardiac arrhythmias are adrenergically induced or sustained. Arrhythmias due to cardiac glycosides also have adrenergic mechanisms. The blocking of β-adrenergic receptors can correct such arrhythmias. Besterman and Friedlander, Rowlands and associates,[4] and Stock and Dale[7] have confirmed the clinical value of β-adrenergic blocking agents in various types of arrhythmia. Unfortunately, however, this beneficial action on disorders of rhythm is accompanied by decrease in coronary blood flow and impairment of the force of myocardial contraction, leading to cardiac failure. Thus, great care is required in the use of these drugs in situations where severe myocardial damage exists and it is of vital importance to define as clearly as possible the minimum effective therapeutic dose. These factors are of particular importance in the treatment of persistent ventricular failure complicating myocardial infarction since extensive muscle necrosis is invariably present.

In the only previous paper on the control of persistent ventricular fibrillation by propranolol the authors used doses ranging from 15 to 22 mg. intravenously. The cardiodepressant effects of the drug were thought to be responsible for the death of one of their three patients. This led them to recommend an upper limit of 10 mg. intravenously.

Our experience suggests that 10 mg. may be unnecessarily high. In all four cases, control of the arrhythmia was achieved by 1 mg. intravenously. In the patients who survived, congestive cardiac failure requiring digitalis and diuretics developed shortly after resuscitation. These patients may well not have survived if larger doses of propranolol had been used. The fact that much smaller intravenous doses of propranolol than previously recommended can be equally effective has been recognized and discussed at a recent symposium.

Our high success rate in controlling this grave complication of acute myocardial infarction in all the cases in which propranolol was used is almost certainly fortuitous. There will be some cases in which neither propranolol nor any other drug in safe doses will control the arrhythmia. The purpose of this paper is to indicate the usefulness and safe dose of propranolol in this grave situation and the success rate is meaningful only in this context.

The point may be made that the last D.C. shock may well have terminated the arrhythmia without the need for propranolol. In persistent ventricular fibrillation it is possible to reverse the fibrillation in the majority of cases. The crux of the problem is to maintain the resulting viable rhythm without allowing it to relapse again into ventricular fibrillation after a short period.

It is for this specific indication that propranolol is advised. A trial of propranolol is well worth while in this situation since the only other recommended line of therapy seems to be internal cardiac massage and defibrillation. This course itself has a great many disadvantages and seems to us to be far more dangerous than the administration of propranolol.

Even when the therapeutic aim, namely, the termination of the arrhythmia, has been achieved, a certain proportion of the patients will die of myocardial inadequacy, as in Case 4 of this series. The massive degree of infarction found at post-mortem examination confirmed that this patient had died of "pump failure" and that the arrhythmia had been a terminal event. The control of the disorder of rhythm could not be expected to alter the prognosis in such cases.

Summary

Four cases of persistent ventricular fibrillation complicating acute myocardial infarction are described. In each case, control of the arrhythmia was achieved by the intravenous administration of 1 mg. of propranolol.

In this dose this drug can be used with reasonable safety in controlling a lethal arrhythmia in patients suffering from extensive fresh myocardial infarctions.

The author wishes to thank Drs. T. Mitchell and J. L. Edwards for their prompt initiation of resuscitative measures; the Charing Cross Hospital Clinical

Resear h Comm ttee for financial help Mrs A Smith Mrs I I Wood nd Mrs C. S March for the lectr ardiogr phy nd monitoring of these patients, d Mrs J Caudle for secretarial as-
ist.

REFERENCES

1 Besterman E M M nd l iedlander D H Cl l experiences w th propranolol Postgrad. M J 41:526 1965
2 H dey H R S Refle tions on cardiopul-monary resuscit tion L ncet 2 1 1966.
3 Parrett, J R and Gra son J Myocardial v scular reacti it after beta-adrenergic block-ade Lancet 1:338, 1966
4 Redding \ T and Rees, J R.: Myocardial vascular react ty Lancet 1:548, 1966.
5 Rowlands, D J Hewitt, G., nd Markma P Propranolol (Inderal) in disturbances of cardiac hythm Brit M J 1:891 1965
6. Sloman, G., Robinson, J S nd McLean, K. Propranolol (Inderal) in persistent ventricular fibrillation, Brit. M J 1:895 1965
7 Stock, J P I and Dale, N Beta-adrenergic receptor blockade in cardiac arrhythmias, Brit. M J 2 1230, 1963
8. Stephen, S \ I wa ted effect of propranolol (discussion) Am. J Cardiol. 18:468 1966.

Clinical pathologic conference

Harvey Wolinsky, M.D.
Johanna VanderBel, M.D.
Louis Cohen, M.D.
Klaus Ranniger, M.D.
Seymour Glagov, M.D.
Chicago, Ill.

Case report

A 61-year-old Caucasian retired school teacher was first admitted to the University of Chicago Hospitals and Clinics on April 1, 1965, with complaints of diarrhea, loss of appetite, weight loss, weakness, and swelling of her lower extremities. *She died on April 4, 1965.*

History. For 25 years the patient had had intermittent episodes of syncope that lasted ½ to 2 hours. She would fall, but would rarely hurt herself during these episodes. No involuntary movements or fecal or urinary incontinence were noted. For five years prior to her admission, the patient had episodes of diarrhea with foul-smelling, occasionally bulky stools. These episodes often followed a period of cramping abdominal pain and were associated with flatulence and at times with vomiting. Lomotil† brought some relief, but relapses occurred approximately every six months. In July, 1964, she entered another hospital, following several weeks of a peculiar sensation in the abdomen and awareness of a movable palpable mass. Tissue obtained by biopsy showed only chronic inflammation and fibrosis, so an entero-enterostomy was performed in an attempt to bypass the obstructed segment. During that hospitalization the patient had four episodes of syncope and hypotension which resembled the episodes which had occurred at home. A normal heart rate was maintained at these times. Although she lost 20 to 30 pounds in the hospital, she regained this weight by the fall of 1964. However, by the end of 1964, the patient had become quite depressed, was markedly anorexic, continued to have diarrhea, and was again losing weight. A trial on a gluten-free diet did not result in improvement of her symptoms. She was hospitalized again in February, 1965, following a brief episode of unconsciousness, described as a petit mal seizure by a nurse present at the time. Results of laboratory tests performed during that hospitalization were as follows: peripheral white blood cells, 10,000 per cu. mm.; hemoglobin concentration, 14.2 grams per cent. *Urinalysis showed a trace of albumin and* an occasional red blood cell. Serum amylase was 50 units (normal 50 to 120), blood urea nitrogen, 36 mg. per cent. Bromsulphalein retention, 37.3 per cent. 24 hour fecal fat, 0.34 Gm. (normal 2 to 6 Gm.). A liver biopsy was reported as unremarkable. Upper gastrointestinal and small-bowel x-ray showed rapid transit of barium. Colon x-ray was essentially unremarkable. The patient was discharged unimproved and her symptoms rapidly became worse at home. On April 1, 1965, two days after she became febrile, she was transferred to the University of Chicago Hospitals. She had an abdominal hysterectomy and left salpingo-oophorectomy in 1958 for fibroid tumors. Both parents had died of tuberculosis before the age of 50.

Physical examination. At the time of admission the patient was depressed and thin with peripheral cyanosis. Blood pressure was 78/60 mm. Hg (right arm recumbent), pulse rate, 96 per minute, temperature, 37.5°C., respirations, 24 per minute. Malar erythema was noted and the tongue was dry. Slight jugular venous distention was present. Auscultation of the chest revealed decreased breath sounds in both bases, but no râles or rhonchi were heard. The heart was not enlarged to percussion. On *auscultation, an occasional* premature beat was heard, S1 and S2 were unremarkable, and a Grade III/VI systolic murmur was heard at the apex. Peripheral pulses were uniformly diminished. Her

From the Departments of Pathology and Medicine, University of Chicago, Chicago, Ill.
The Conference was arranged and directed by Dr. Glagov.
The work by Dr. Glagov was done during the tenure of an Established Investigatorship of the American Heart Association.
Address: Department of Pathology, University of Chicago Hospitals, Chicago, Ill.
†G. D. Searle and Co., Chicago, Ill.

abdomen w distended, but the liver palpable 8 cm below the right costal marg in the midclavicu lar l'ne, had smooth edge nd was slightly tender Neither he pleen nor any abdom nal masses were palpable N guard ng was present the bow l sounds were normal

On ex mination of the genitalia, marked erythema of h labial mucosa was noted The remainder of h pelvic exam nation was not remarkable. Pitting edema of both lower extremities was present (2+ to 3+) and both calves were slightly tender Neurologic examination revealed symmetrical deep tendon reflexes no pathologic reflexes were elicited. Muscle trength was generally diminished

Laboratory data Peripheral leukocytes, 13,200 per cu mm hemoglobin oncent tion 13 1 grams per cent red blood lls 4 27 million per cu mm hematocrit, 44 per cent platelets 185 900 per cu mm, reticulocytes 1 7 per cent and total eosinophils 425 per cu mm Th differential count was as follow neutrophils 79 per ent small lymphocytes 11 per cent monocytes, 5 per cent eosinophils, 5 per ent Urinalysis pH 5.5 specific gra ty 1 022 protein 1+ *no reduction* few gr lar cast nd 2 t 3 white cells per high-power field Fasting blood sugar was 80 mg per cent serum sodium 135 mEq per liter serum potassium 4 3 mEq per liter serum hloride, 92 mM per liter serum CO_2, 23 4 mM per liter serum calcium, 8 9 mg per cent serum phosphorus, 3 7 mg per cent serum alkaline phosphatase, 5.2 units per cent (normal 1 5 t 4) total plasma proteins, 7 1 Gm. per ent albumi 2.3 Gm. per cent globulin, 4.8 Gm per cent The blood ure itrogen concentra tion was 31 mg per cent Total serum bilirubi w 1 0 mg per cent direct, 0 7 mg per cent thymol floc lation, 1+ thymol turbid ty 2.7 Serum lactic dehydrogenase was 1,010 units glut mic-oxaloacetic transaminase 124 n ts glutamic-pyruvic transaminase, 122 nits

The patient condition deteriorated rapidly Her systolic blood pressure remained below 90 mm Hg On April 3 1965 a left thoracentesis wa performed, and 500 c.c. of yellow lear fluid with a specific gravity of 1.012 w removed smears revealed no microorganism. Upon return from a chest x-ray examination after the thoracentesis, no blood pressure read'ng could be obtained Jugular ei distention was present when the patient was seated inlined t 45 degrees digitalis was administered. N fluid was obtained from an ttempted pericardiocentesis. After this, the patient bega to vomit dark brown material. The blood pressure remained low and heart sounds were barely udible. Vasopressor agents were used to no vail her pupils became dilated and she died.

X-ray examination (Dr Klaus Ranniger). The chest x ray on admission here i April, 1965 show left pleural effusion and probably small pleural effusion on the right as well (Fig 1 *A*). The heart is of normal size. The film of the bdomen show diffuse ground-glass appearance suggestiv of ascites and slightly d'lated loop of small bowel in the midabdomen (Fig 1 *B*). N upper gastrointestinal examination was done *during* her hospitalization here no outside films accompanied the patient.

Discussion

DR COHEN Although the patient was apparently well for the first 36 years of her life syncopal episodes lasting from ½ to 2 hours occurred between ages 36 and 61 This is the first problem which requires our attention. The second problem is the nature of her gastrointestinal disorder i.e. her complaints of cramping abdominal pain diarrhea, nausea, vomiting and foul

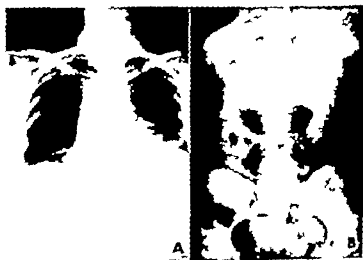


Fig 1 *A* The frontal chest film shows left pleural effusion. The heart is of normal size *B* The abdominal film show a diffuse ground glass appearance indicat ve of ascites. A single loop of slightly distended small bowel is seen.

bulky stools during the last five years of her life. The third problem to be considered is the nature of her terminal illness.

Let us discuss the syncope first. The possible causes can be divided into two groups: those of cardiovascular origin and those of neurological origin. Neurological syncope can be attributed to anatomic lesions or functional chemical disorders. What possible chemical derangements could result in syncope of up to two hours duration occurring over a 25 year period? Severe hypoglycemic episodes could be responsible. However, convulsions are usually associated with hypoglycemic coma, and these were not a feature of her clinical history. The absence of convulsions and the repeated occurrence of syncope over a period of 25 years make hypoglycemia an unlikely possibility. Could this woman have had episodes of hypoxia? Could she have somehow been exposed to some environmental factor which resulted in repeated syncope? There is no evidence to support these possibilities. Did she have a hyperventilation syndrome? Decreased CO_2 in the blood resulting from hyperventilation could result in reduced cerebral blood flow since CO_2 is a potent vasodilator of the cerebral blood vessels. In addition, the respiratory alkalosis associated with hyperventilation will lower blood ionized calcium levels which can result in syncope. However, the patient had no tetanic convulsions, which would have reflected the hyperirritability of nerve and muscle related to decreased ionized calcium levels. The long duration of the symptoms also makes this possibility unlikely.

What anatomic lesions could be responsible for neurological syncope? The sudden onset of syncope at age 36 suggests the presence of primary or metastatic intracranial tumor, but again the 25 year duration stands against this. What about congenital or acquired vascular disease? A congenital vascular anomaly would be unlikely to produce syncopal episodes for 25 years; acquired disease, particularly occlusive disease of the branches of the vertebral or the internal carotid arteries, would also be quite unlikely to be present for such a long time without the appearance of convulsions or a cerebrovascular accident. A cerebral scar, due to past, forgotten trauma, might serve as a focus for akinetic seizures. Idiopathic seizures usually have their onset at an earlier age.

Cardiovascular causes of the syncope include simple syncope, i.e., peripheral vasodilatation due to some "fright or delight," or a vasovagal reaction which could produce a severe bradycardia. Again, the long duration of symptoms and the persistently normal heart rate during the episodes eliminate these possibilities. Complete atrioventricular block punctuated by periods of asystole should produce convulsions at least occasionally, but would probably not recur over a 25 year period. Other causes of reduced cerebral perfusion such as the vagotonia, carotid sinus stimulation, or arrhythmias are also unlikely to continue for 25 years. Orthostatic hypotension should also be mentioned in passing. It can be present in some patients with neuropathy, generalized vascular disease (usually atherosclerotic), after long confinement to bed, or during treatment with ganglionic blocking agents. I, therefore, consider the most likely cause of her syncope to be a cerebral scar, independent of the events in the last five years of her life.

The outstanding problem of the last five years of her life was her gastrointestinal symptomatology. The weight loss, diarrhea, and bulky, foul-smelling stools suggest a malabsorption syndrome. An acquired enterocolic fistula as a result of inflammatory or neoplastic disease, trauma, or some sort of functional neuromuscular hypermotility could have produced a rapid transit of food through the gastrointestinal tract which we know occurred in this individual. A fistula in the region of her enteroenterostomy, for example, could account for malabsorption, but her symptoms began prior to that surgery, so that another cause must be sought.

Malabsorption could be due to a non-β cell islet adenoma of the pancreas which is presumably capable of secreting gastrin, stimulating the stomach to produce excessive amounts of hydrochloric acid and altering the pH of the small bowel so as to prevent activation of pancreatic and other digestive enzymes and resulting in malabsorption. This disorder has been called the Zollinger-Ellison syndrome. Other features include jejunal ulcers and multiple

endocrine adenomas involving the para thyroid pituitary and adrenal glands. Evidence in favor of this diagnosis is lacking. No mention is made of the acidity or volume of gastric secretions and gastrointestinal x rays taken elsewhere were not remarkable.

Another possibility is obstruction of the common bile duct for bile salts are necessary for emulsification of fat and the adequate absorption of the fat soluble vitamins A E D and K. We are given little information about the status of this woman's liver function. Although she was presumably never icteric. Bromsulphalein retention was increased during one of her last hospitalizations. However her abnormal liver function tests during the terminal illness may be explained adequately on a different basis her hepatic insufficiency was not serious enough to account for a malabsorption syndrome.

What about the pancreas Usually malabsorption results only from extraordinary destruction of pancreatic tissue. Nevertheless, multiple episodes of acute pancreatitis could account for the attacks of acute abdominal cramping pain and her diarrhea and malabsorption could have resulted from destruction of pancreatic parenchyma. Some evidence for this hypothesis was found at the time of the surgery which was performed to clarify the nature of the palpable abdominal mass, for a tumor was seen which appeared to be originating in the pancreas. This could have been a pancreatic cyst. Since the biopsy showed only chronic inflammatory tissue histologically the underlying disease remains obscure but chronic pancreatitis or a neoplasm involving the pancreas cannot be excluded as the basis of her abdominal symptoms and her malabsorption.

Celiac disease was suspected at one time for her physicians removed gluten from her diet for a period of time. Individuals with celiac disease exhibit a peculiar and exquisite sensitivity to inclusion in their diet of gluten a protein found in wheat barley oats, and rye. The removal of gluten from this patient's diet did little to ameliorate her symptoms. Stasis of food trapped in a normally sterile segment of small bowel could favor bacterial growth interfering with absorption of vitamins and nutrients this results in the so-called *blind loop syndrome*. In this patient, such a loop could have been produced surgically inadvertently or could have resulted from an intestinal inflammatory process, perhaps associated with pancreatitis or some other chronic intra abdominal disease.

Other less common diseases of the small intestine which are associated with malabsorption include *lymphangiectasia* a disorder in which intestinal lymphatic channels are abnormally dilated and *acanthocytosis* a disorder in which an unusual spiny erythrocyte is associated with anemia malabsorption and β-lipoproteinemia. She was not anemic and we do not have information concerning her blood lipids. Also these diseases tend to occur in young patients. *Amyloidosis* primary or secondary *scleroderma* and *disseminated sarcoidosis* are other uncommon causes of malabsorption which could be mentioned but for which evidence is lacking. *Disaccharidase deficiency* is another unlikely cause because of both the severity and age of onset of her symptoms. *Whipple's disease* can also be excluded in the absence of lymphadenopathy or arthritis. *Regional enteritis* should be mentioned but she was not anemic and involvement of the small intestine seemed to be limited to the proximal portion. *Lymphoma* of the small bowel can cause malabsorption but in the absence of lymphadenopathy enlargement of her spleen or lymphocytosis it should be ruled out.

I have already alluded to one neoplastic disorder associated with endocrinopathy the *Zollinger Ellison syndrome*. I would now like to discuss another the *carcinoid syndrome* in which the neoplasm is a metastatic carcinoid tumor. The *carcinoid syndrome* can produce hypermotility of the bowel with diarrhea and episodes of hypotension both of which were prominent in the patient. The peripheral vasodilatation associated with this disease may be confused with peripheral cyanosis, and about 50 per cent of patients with carcinoid syndrome have conspicuous violaceous facial flushing. About 50 per cent develop pulmonary stenosis as a consequence of endocardial and valvular fibrosis on the

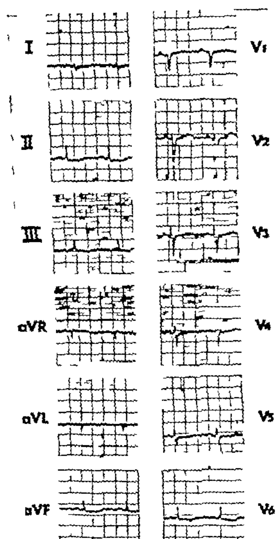


Fig. 2 The ECG on Feb 25 1965 shows QRS axis of +90 degrees and flattened T waves in Leads I AVL, V V and V T waves in V are inverted

right side of the heart. This patient had a malar flush and we are told that she also had a red erythematous vulva in the carcinoid syndrome erythema of all mucosal surfaces is not uncommon. Thus the carcinoid syndrome could explain many of our patient's symptoms including the malabsorption syndrome liver metastases could have produced the hepatomegaly and resulted in ascites.

Finally I wish to discuss her terminal illness. We are told that the patient had bilateral peripheral edema and that the skin of the lower extremities was shiny and smooth This is evidence of bilateral venous thrombosis in the iliac or femoral veins in a chronically ill woman with a reduced intravascular volume who has been confined to bed Multiple episodes of pulmonary emboli could have accounted for her pleural effusions and some of her terminal hepatomegaly The extraordinarily high serum enzyme levels indicate that severe hepatic central venous congestion with necrosis was occurring Since the pleural effusion could have been partly due to pancreatitis, determination of the amylase content of the pleural fluid would have been helpful

The electrocardiogram (ECG) taken elsewhere three months prior to her death (Fig 2) reveals a sinus rhythm and normal atrioventricular conduction a QRS axis of +90° and minor nonspecific ST changes in the left lateral leads. These findings support the diagnosis of pulmonary embolism The only ECG taken here (April 1965) showed low voltage in all leads, which is compatible with the presence of a pleural effusion

The patient's total hospital stay here prior to her demise was only three days and surely her fate was sealed before she came to the hospital Many of the features of her terminal illness could be manifestations of recurrent pulmonary emboli possibly with massive embolization at the very end Her symptoms during the last five years of her life could be due to a pancreatic cyst and multiple episodes of acute pancreatitis leading to pancreatic insufficiency Nevertheless, I am still intrigued with the possibility that this is a case of the *carcinoid syndrome* and that the biopsy of the tumor at laparotomy was inadequate Had the patient lived longer the diagnosis of carcinoid tumor might have been established by measurement of the 24 hour urinary excretion of 5-hydroxyindole acetic acid a liver biopsy and repeated careful cardiac auscultation. The pulmonary stenosis murmur is an ejection-type flow murmur an associated thrill over the pulmonic area may be present. Of course the presence of both the murmur and the thrill depends on adequate flow their absence in this case could be explained by hypotension. Another sign of pulmonary valve disease is a single second heart

sound presumably resulting from impaired movement of the diseased valve

DR. GLAGOV If indeed this were a case of the carcinoid syndrome, would the heart lesions usually seen in this disease be sufficient to explain the ascites and the pleural effusion?

DR. COHEN The right axis deviation seen on the outside ECG is consistent with that possibility It is perfectly possible that most of the cardiovascular symptoms resulted from pulmonic valve stenosis and/or tricuspid valve lesions such as are seen in the carcinoid syndrome. However the murmur described was located at the apex not in the pulmonary area, where I would have expected it to be if there were a predominant pulmonary valve lesion If the right heart were involved as it is in the carcinoid syndrome it could explain the pleural effusion hepatomegaly ascites, peripheral edema, and the electrocardiographic right-axis deviation As a matter of fact, the moderately severe hepatic function abnormalities could be attributed to the combined effects of extensive liver metastases and chronic passive congestion due to congestive heart failure.

DR. GLAGOV I am told that the physicians who saw her terminally also were very confused by the murmur

DR. MALCOLM PAGE Although a murmur of pulmonary stenosis is characteristic of the *carcinoid syndrome* I might add that in a number of series [3] a tricuspid insufficiency murmur was of equal prevalence with a pulmonary stenosis murmur

AUDIENCE QUESTION How common is it for an islet-cell tumor to cause malabsorption? Could an islet-cell tumor explain the many years of syncope?

DR. COHEN Zollinger and Ellison called attention to the syndrome in 1955 the number of reported cases totaled 260 by 1964 [4] In these reports, the tumor did not regularly cause diarrhea I believe that it is probably responsible for only a very small fraction of the total number of cases of malabsorption. Your second question deals with the possible relationship between the syncope and the Zollinger Ellison syndrome. In these non-β' islet cell adenomas, the α γ or δ cells may secrete gastrin but hyperinsulinism is not seen in this disorder [4]

DR. GLAGOV Let us proceed to the pathologic findings in this fascinating case

DR. VANDER BEL At autopsy the body was that of an emaciated elderly woman the abdomen was distended and there was cyanosis of the malar area and of the neck. The skin of the upper anterior chest was telangiectatic. The palms of the hands and the fingertips were cyanotic both lower legs were edematous. 2½ L. of fluid were found in the abdominal cavity and 1 000 c.c. of fluid in the left pleural cavity The loops of the small intestine were matted together by fibrous serosal adhesions. The heart weighed 300 grams both right chambers were dilated particularly the right atrium The endocardium lining the ventricles was intact, but the endocardium lining the atria was thickened and opacified Except for the aortic valve the valve leaflets were markedly deformed The mitral valve (Fig 3,*A*) was 8.5 cm. in circumference with thickened leaflets and shortened thickened chordae tendineae the posterior leaflet was more involved than the anterior leaflet. The tricuspid valve (Fig 3,*B*) measured 12.5 cm leaflets were thickened and shortened and chordae tendineae shortened and thickened The pulmonic valve was most severely involved (Fig 4,*B*) thickened and fused leaflets resulted in both stenosis and insufficiency with a luminal cross-sectional area of ap-



Fig 3 *A* Mildly fibrotic and stenotic mitral valve *B* Severely fibrotic and insufficient tricuspid valve.

proximately 1 sq cm. The distribution of the valve lesions was not typical of rheumatic heart disease, for despite severe alteration of the pulmonic valve the aortic valve was spared (Fig 4,A) The microscopic appearance of the valve lesions were more characteristic of carcinoid heart disease than of rheumatic heart disease. A section of the pulmonic valve stained with hematoxylin and eosin (Fig. 5,A) shows only marked sclerotic thickening of the leaflet. However special stains reveal that the deformity and thickening of the valve leaflet is not due merely to scarification by increased collagen and elastin but results primarily from an accumulation of ground substance in loose connective tissue containing both acid and neutral mucopolysaccharides. This material appears as an accretion on the valve surface and leaves a discernible underlying valve structure (Fig 5,B and C) as has been described in carcinoid heart disease by others. In contrast rheumatic heart disease results in marked destruction of valve structure and replacement of valve substance by scars including both collagen and elastin conservation of a valve skeleton within the lesion is rarely seen The microscopic appearance of the tricuspid and mitral valves in this case was similar to that of the pulmonic valve but changes were not as severe



Fig 4 A Normal aortic valve. B Stenotic and fibrotic pulmonary valve

In addition to the lesions of the cardiac valves, there were subendothelial thickenings of the anterior descending branch of the left coronary artery (Fig 6,A) and the superior vena cava (Fig 6,B) as well as fibrinoid necrosis of small intramyocardial arteries (Fig 6 C) The subendothelial thickenings of the vena cava and coronary artery were similar no siderophages or cholesterol clefts, characteristic of atherosclerosis, were seen. The myocardium was diffusely infiltrated by lymphocytes and atrophic muscle fibers were numerous. The exact nature of these changes were not clear and could reflect prolonged ischemia or associated viral myocarditis.

The liver weighed 2 000 grams and was approximately 40 per cent replaced by nodules of firm grayish white glistening tumor nodules with focal hemorrhagic areas but no evidence of softening or necrosis. The microscopic appearance of

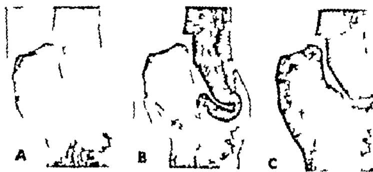


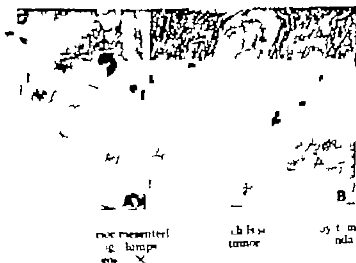
Fig 5 Markedly thickened pulmonary valve. A Hematoxylin and eosin stain B Verhoeff-van Gieson stain C Alcian blue P A.S. stain. (X7)



Fig 6 A A terior descending branch of the left coronary artery with greatly thickened i tima. (Verhoeff-van Gieson × 30) B Superior ena cava w th similarly thickened tima. (Verhoeff van Gieson × 30) C, Small branch of coronary artery with fibrinoid necrosis i the media (P A S. × 450)



Fig 4 Gross appearance of the 1.0 cm primary arcinoid lesion in the small bowel. B Microscopic appearance of the primary carcinoid tumor the w ll of the small bowel. (Hematoxylin and eosin × 20) C, Detailed microscopic appearance of the primary tumor (Hematoxylin and eosi × 350) D Detailed microscopic p-pearance of hepatic metastasis of carcinoid tumor (Hematoxylin and eosi × 350)



mor mesenteri g lump s ×

th is tumor

t mor nd fibrous tissue nda t fibrou tissue su

the neoplastic tissue was characteristic of carcinoid tumor: uniform small cells were arranged in nests which were separated by delicate fibrous strands (Fig. 7,*D*). In some nests small glands could be discerned. Acute and chronic passive congestion, fatty change, and mild pericholangitis were evident in liver sections without tumor tissue. The pancreas was grossly and microscopically normal. About the presumed site of the abdominal surgery the superior mesenteric artery was surrounded by firm gray white tissue (Fig. 8,*A*). Microscopically, carcinoid tumor resembling that seen in the liver encircled the artery (Fig. 8,*B*). However, nearby relatively acellular sclerotic hyaline tissue was abundant and tumor cells were scant; the biopsy could well have been taken from such a fibrous area. Metastatic carcinoid tumor nodules were found in the ovary and in periaortic, peripancreatic, and mesenteric lymph nodes. The only lesion which could have been the primary focus was a round nodule projecting from the mucosal surface of the small intestine 90 cm. from the ileocecal valve. It measured 1.0 cm. in diameter and had a central depression (Fig. 7,*A*). The cut surface of the nodule was gray white and microscopic examination revealed a carcinoid tumor nearly identical to that described in the metastatic sites (Fig. 7, *B* and *C*). It had extended into the muscularis and serosa, causing marked local thickening of the bowel wall. The site of surgical anastomosis was healed without any evidence of anatomic obstruction. No other abnormalities of the intestines were found. Attempts to stain both the primary and metastatic tumor tissue for argentaffine granules with the Fontana Masson and Diazo stains were unsuccessful, but this does not exclude the diagnosis of carcinoid tumor in the presence of such characteristic morphology.

In summary, this woman with a clinical history of diarrhea, episodes of hypotension, malar erythema, and subsequent right ventricular failure had metastatic carcinoid tumor. A small infiltrating intestinal tumor was probably the primary site. The abdominal metastatic tumor tissue about the mesenteric artery was densely sclerotic so that the biopsy at laparotomy probably did not contain recognizable carcinoid tumor. The cardiac lesions were characteristic of carcinoid heart disease and included endocardial thickening involving both atria and the pulmonic, tricuspid, and mitral valves. Functionally, the aortic valve seemed normal, the pulmonic valve stenotic and insufficient, the mitral valve insufficient and possibly stenotic, and the tricuspid valve insufficient. The right ventricle was dilated. Edema, ascites, and passive congestion of the liver had resulted from right ventricular failure. The inflammatory reaction in the myocardium and the changes in the small coronary artery branches remain without a definite explanation. I cannot provide an adequate organic explanation for the syncope, especially since examination of the brain was not permitted. However, the syncope could be associated with the hypotensive episodes which accompanied the carcinoid syndrome in this patient. No diffuse gross or microscopic lesions of the intestine which could be associated with malabsorption were found. Again, this disturbance could be attributable to functional consequences of the diarrhea associated with the carcinoid syndrome. A blind loop syndrome can probably be excluded, especially since episodes of hypotension and diarrhea antedated her surgery by four years and the anastomosis was anatomically intact. The abnormal liver function tests may be attributed to the widespread metastases and the chronic passive congestion.

DR. COHEN: I might add that the cramping abdominal pain could be related to the fibrotic process about the superior mesenteric artery which may have resulted in intermittent intestinal ischemia.

REFERENCES

1. Thorson, A., Biorck, G., Bjorkman, G., and Waldenström, J.: Malignant carcinoid of the small intestine with metastasis to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. A clinical and pathological syndrome, Am. Heart J. 47: 795, 1954.
2. McDonald, R. A.: A study of 356 carcinoids of the gastrointestinal tract, Am. J. Med. 21:867, 1956.
3. Thorson, A.: Studies on carcinoid disease, Acta med. scandinav. (Suppl.) 334: 122, 1958.

4. Ellison, E. H., and Wilson, S. D.: The Zollinger-Ellison syndrome: reappraisal and evaluation of 260 registered cases, Ann. Surg. 160:512, 1964.
5. Zollinger, R. M., Elliott, D. W., Endahl, G. L., Grant, G. N., Goswitz, J. T., and Taft, D. A.: Origin of the ulcerogenic hormone in endocrine induced ulcer, Ann. Surg. 156:570, 1962.
6. Roberts, W. C., and Sjoerdsma, A.: The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease), Am. J. Med. 36:5, 1964.
7. Wenger, R.: Ein Fall von Endokardfibrosierung bei Karzinoidsyndrom, Ztschr. Kreislaufforsch. 51:(2) 123, 1963.

Fundamentals of clinical cardiology

The Master two-step test

Arthur M. Master, M.D.
New York, N. Y.

In this review of the practical and the latest developments of the two-step exercise test we will stress (1) the *need* for the test and for *standardization*, (2) the *procedure* for its performance, (3) our *criteria* of an abnormal test, and (4) the place of the test in the discovery of the vast complex of completely *silent coronary artery disease*. The illustrations are new for the most part, but some have been previously published (see table and figures).

Need and standardization

In the diagnosis of coronary artery disease, whether the symptoms are atypical (Figs. 5 and 6) or completely absent ("silent") (Figs. 8 and 20 to 23), the 12 lead resting electrocardiogram (ECG) is the most important means we possess. The resting ECG, however, will not resolve the difficulties. If it were always abnormal it would probably be the answer, but that is not the case. Even in classical angina it has been shown that the ECG is negative in 47 to 83 per cent of the cases (Figs. 8 to 10, 12, and 13). We at times have found it normal in 47 per cent, whereas Doyle at the Albany Medical School, in an epidemiological study, has reported that 83 per cent of his patients with angina pectoris possessed normal resting ECGs. Hence a negative resting ECG is far from excluding disease of the coronary arteries.

The history is not always helpful. Certainly, if one sees, in a man 55 years old, pressure in the breastbone which is related to effort, walking after meals, walking in the cold, or walking against the wind, lasting but 2 or 3 minutes and relieved immediately by nitroglycerin, one does not go further. It is coronary disease. Similarly, if one sees a nervous 38-year old woman who complains of an ache over the precordium, and this is more or less continuous, not brought on by any cause whatsoever, not relieved by nitroglycerin, one also need not go further. Between these two extremes there are very many patients in whom the pain or pressure is atypical or completely absent. We have written to great extent on these two points and will therefore be brief.

Significant coronary disease may be completely asymptomatic (Figs. 8 and 20 to 23). This has been demonstrated by epidemiological studies, by postmortem examination, by routine examination of pilots, and the like. Daily the author sees patients with completely silent disease. An abnormal resting ECG or a positive two-step test has been discovered by insurance physicians, by airline medical directors, by executive health examinations, and by the military medical corps.

Anyone who is responsible for the lives of others—as, for example, bus drivers, train engineers, policemen—should have a functional test of the heart. The two-

Emeritus Clinical Professor of Medicine, The Mt. Sinai School of Medicine; Consultant Cardiologist, The Mt. Sinai Hospital, New York, N. Y.

step test would discover latent coronary disease. All airplane pilots, everyone in military service, in fact all men and women over 35 should have annually a physical examination, a teleoroentgenogram of the chest, a resting ECG, and if that is normal, a two-step test or its equivalent.

No apology need be offered for the foregoing because it must be clear to the reader that coronary disease is the most important killer and morbidity producer in the civilized world. In the United States alone 600,000 deaths yearly are attributed to coronary disease.

When the amount is $25,000 or more the insurance companies do the two-step test if the resting ECG is normal. (Dr. Charles Berry told us that he does the two-step test on his astronauts.)

An important function of the two-step test was demonstrated recently at a conference on standards of physical fitness of aircrew which was held on Nov. 6 and 7, 1965, and which was reported in the *American Journal of Cardiology* for October 1966 (vol. 18, pp. 630 to 636). In this meeting were medical representatives of airlines, the Federal Aviation Agency, insurance companies, the United States Air Force, the Naval Aviation Physical Qualifications Board, and the United States Public Health Service, and also civilian cardiologists. The following recommendation was made: A routine electrocardiogram should be performed on all aircrew prior to initial certification, age 35 years, and annually from age 40. This should include a standard 12 lead recording obtained with an adequate electrocardiographic machine and also a double Master's test or a progressive type of exercise.

Table I. Trips performed in Master double two-step exercise test (figures for male patients are followed by those for female patients in parentheses)*

Weight (lb.)	Age (yr.) 15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
50–59	64(64)												
60–69	62(60)												
70–79	60(55)												
80–89	58(56)	58(56)	58(56)	56(54)	54(52)	54(49)	52(48)	50(47)	50(42)	49(42)	46(40)	40(35)	44(36)
90–99	56(52)	56(54)	58(52)	54(50)	54(45)	52(46)	50(44)	50(44)	49(42)	46(40)	44(39)	44(39)	42(37)
100–109	54(50)	56(52)	56(52)	54(50)	52(45)	50(46)	50(44)	45(42)	46(40)	44(38)	44(36)	42(36)	40(34)
110–119	52(47)	54(50)	54(50)	52(49)	50(46)	50(44)	49(42)	49(40)	46(38)	44(36)	42(36)	42(34)	40(32)
120–129	50(44)	52(49)	54(49)	52(46)	50(44)	48(42)	46(40)	46(39)	44(38)	42(36)	40(34)	40(32)	38(30)
130–139	49(40)	50(48)	52(46)	50(44)	49(42)	46(40)	46(38)	44(38)	44(36)	40(34)	40(32)	38(30)	36(30)
140–149	46(38)	45(44)	50(44)	49(42)	49(40)	46(38)	44(39)	42(36)	40(34)	40(32)	38(32)	36(30)	38(29)
150–159	44(34)	49(42)	50(40)	48(40)	46(38)	44(38)	42(36)	40(34)	40(32)	38(32)	36(30)	36([illegible])	34(29)
160–169	43(32)	46(40)	49(35)	46(36)	44(36)	44(36)	42(34)	40(32)	38(32)	36(30)	36(29)	34(26)	34(24)
170–179	40(29)	44(39)	46(36)	46(36)	44(34)	42(34)	40(32)	39(32)	36(30)	36(25)	34(26)	34(26)	32(24)
180–189	38(26)	42(36)	46(34)	44(34)	42(34)	40(32)	38(32)	38(30)	36(25)	34(25)	32(26)	32(24)	30(22)
190–199	38(24)	40(34)	44(32)	42(32)	42(32)	40(30)	38(30)	36(29)	34(26)	32(26)	30(24)	30(26)	29(22)
200–209		36(32)	42(30)	42(30)	40(30)	38(29)	36(29)	34(26)	32(26)	32(24)	30(22)	[illegible](22)	[illegible](20)
210–219		36(30)	42(29)	40(29)	38(29)	36(26)	34(26)	34(26)	32(24)	30(22)	29(22)	29(22)	28(20)
220–229		34(25)	40(26)	40(26)	38(26)	36(26)	34(24)	32(24)	30(22)	28(22)	28(20)	28(20)	24(18)

*Master, A. M., and Rosenfeld, I.: The "two-step" exercise test brought up to date, New York J. Med. 61:1850 (June 1) 1961; Dis. Chest 51:347, 1967.

The physical background of the patient is unimportant for the two-step test. The two-step test is for myocardial ischemia and not for physical fitness." The latter is an entirely different matter and requires much more strenuous exertion than does the two-step test. On the other hand no matter what the physical background of the patient is, if he suffers from ischemic heart disease, the two-step test will be positive whether he has always been an athlete or a prize-fighter or has been most sedentary.

We have repeatedly written that a test for coronary disease must be *standardized*. We found very early when the test was evolved at Cornell University Medical College between the years 1925 and 1929 that the response to exercise (blood pressure and pulse rate) varied with the age weight and sex of the individual. The older the individual the less efficient was his heart. It was at maximum efficiency between the ages of 22 and 30 years in men and it was about the same in women. The men could perform about 3,300 foot pounds of work per minute at their highest efficiency and the women about 3,100. Above these ages cardiac efficiency declined. Above the weights of about 160 pounds for men and 145 pounds for women again cardiac efficiency decreased.

If the standardized test is used one can employ it anywhere in the world and the results are comparable provided it is performed as we will describe. Untold modifications of the two-step test have been made but these are *not* the two-step test. The test should first be done on healthy persons for controls. We performed hundreds and hundreds of tests on normal persons in 1925 through 1929. The tables were constructed on the basis of these tests (see Table I).

Physiological and pharmacological experiments on human subjects are possible if the test is standard. We evaluated proniazid (Marsilid) which was first used in the treatment of tuberculosis, and later used by the orthopedic surgeons and then by psychiatrists. We found for example that although the classical anginal syn

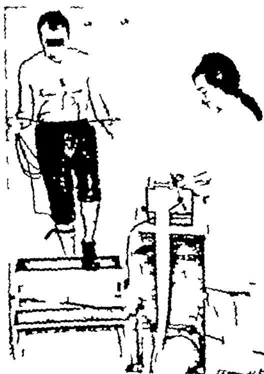


Fig. 1. Administering the two-step test (From Dis. Chest 51:347, 1967).

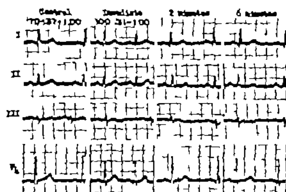


Fig. 2A. F. C., 48-year-old man (No. 18469 M) had chest pain of unknown cause. Results of the double two-step test were negative. The QT remains at resting value of 1.00 after exercise despite increase in rate from 70 to 100 per minute. Search for extracardiac causes of chest pain revealed extensive cervical and dorsal spondylitis with discogenic disease.



Fig. 2B. Same patient as in Fig. 2A. He is still perfectly well 20 years later. Once he was assured he had no heart disease he lost all concern for the chest pain.

drome was entirely lost when the patient was taking this drug, his coronary disease remained. The two-step test was just as dramatically positive as it had been when he had been having symptoms—before he took the iproniazid (Fig. 8).

Perhaps the most important bit of evidence that the two-step test should be

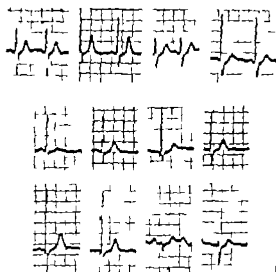


Fig. 3. All these "j" depressions are within normal limits. They return to the baseline quickly within the 50 per cent limit of the electrical systole, that is, before one half of the QT interval. However, no measurement of the QT ratio is necessary; visual inspection is sufficient. (From Dis. Chest 51:347, 1967.)

standardized comes from the monitoring of our patients (Figs. 11 and 19). We have been doing this for five years, and have monitored more than 1,000 patients in that time. We have recorded the ECG while the patient walks over the steps. Again and again the ECG at the first few trips will be unchanged, then slight "j" (junctional) depressions of the RS-T segment will appear, these will become deeper and finally ischemic changes will be observed—but only at the very end. For example, if the table calls for 42 trips it will be perhaps on trip 39 that ischemic RS-T depressions will first appear. This is not to say that every case of angina, for example, will show this, but we feel that in at least half the patients we find evidence that the full number of trips must be performed before the test becomes positive.

That the single two-step test, that is, the minute and a half of exercise, may be negative and the "regular" or three-minute test be positive is an old story (Fig. 18). Again and again, in examining a patient whom we felt had severe coronary disease, we started with the single test. If that were negative, an hour later

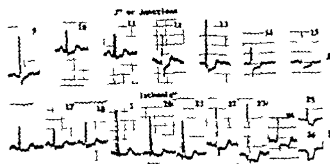


Fig 4 4 In the upper row are j changes. They ar signific t changes beginning with the equivocal lterations (no 9) to the near "ischemic depressions in the last four illustrations. The first three may be equivocal, but there is no doubt that the last four are abnormal. This, again, can be decided by usual inspection *B* The ischemic RS-T segment depressions ar seen in nos. 16 t 26 The first is merely ½ mm. depressed, the second of about ¾ mm. The remainder are obviously abnormal th either horizontal or sag depression of more than 1 mm. Although good many and even we ourselves might consider the first example of doubtf l significance, w ould interpret the second as significant.

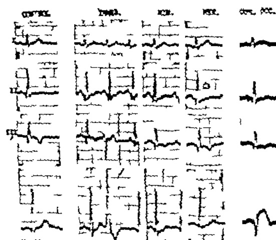


Fig 5 8. A 38-year-old man was dark, nervous gypsy He had had heaviness across the chest for three months, not related t effort Results of physical examination x-ray and fluoroscopic examination and 12 lead resting ECG ere negative. A t o-step test taken on March 7 1949 yielded positive results with premature beats and RS-T depressions in Leads V and II after exercise There are Q w es in Leads II and III hich may ha e indicated previous m ocardial infarction. Because of the severe heaviness, only single two-step test as essayed It abnormal There were ischemic RS-T depressions in the 2 minute Lead III nd there ere significa t j in the 2 minute Lead V V occasional entricular premature contraction appeared

That the positiv test as significant was substantiated by oronary occlusion hich occurred 3 weeks later (see right hand column). A Q wa as present in Lead V with RS-T elev tion in Leads I and V (The RS-T segment is depressed in II and III and diphasic T w re is seen in I V and V) The patient died 2 year later of heart ttack.

or the next day we performed the double It was then abnormal

We have often seen instances where for one reason or other the full number of trips was not performed and the test was negative For example, when exam ining a man, a nurse technician employed the usual number of trips for women (a lower figure) instead of that for men and the test was negative When t was re peated w th the correct number of tr ps it became positive It would appear that, n many patients with severe coronary disease too little exertion would be in

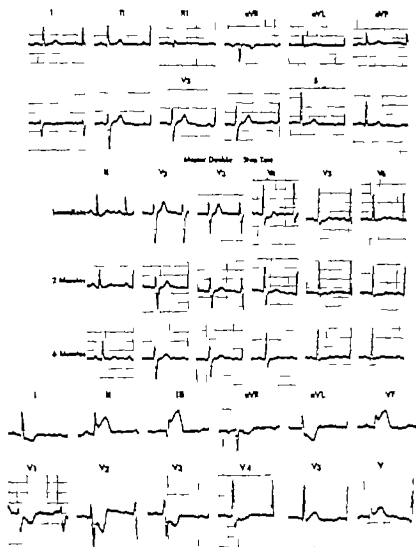


Fig. 6. G. G., 51-year-old man, had substernal pressure on exertion which was never relieved by nitroglycerin. For this reason the family doctor doubted that he had coronary artery disease.

The resting ECG (upper two rows) was completely normal.

The double two-step test revealed only $\frac{1}{2}$ mm. "ischemic" ST depressions in the 2 minute Lead V_4. That this was significant, however, was confirmed by an attack of severe chest pain 2 months later. The ECG was characteristic of transmural infarction; there were almost monophasic elevations of the RS-T segment. The patient died 5 minutes after this record was made.

The degree of ischemic ST depression after the two-step test correlates with the severity of coronary disease only in a general way, but occasionally an ischemic ST depression of only $\frac{1}{2}$ mm. is significant. In fact, any ischemic depression should produce concern unless the clinical findings disprove it. (From Dis. Chest 51:347, 1967).

sufficient to make the test abnormal. On the other hand, if a healthy person is overexercised, ischemic RS-T depressions may appear in the ECG. There is overwhelming evidence in the literature that if even normal people are exercised to extremes they will show ischemic RS-T depressions. Hence this is more evidence of the need for standardization.

If the standardized table is followed the test will be found to be completely safe, especially if the doctor does not perform it when there is obviously an impending infarction and above all if the patient is admonished to stop if he develops any discomfort, pressure, or pain in the chest or arms. This makes for complete safety. That is why in the thousands of tests

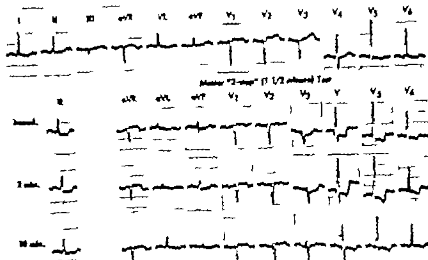


Fig 7 M M 60-year-old man as in status anginosus I add too he had very severe cervical and upper dorsal arthritis If he merely moved his torso or turned his head he developed substernal pain. He had suffered previous anteroseptal all myocardial infarction as evidenced by the Qs pattern in V₁-V H as made by positive road th 1st but this was of no a ail.

Only single two-step test as performed It was dramaticall positi

A few months after the two-step test was done, the patient as operated upon The upper 5 left dorsal ganglia nd the stellate ganglion ere removed and cardiopericardiopex as performed The patient died 3 ½ weeks after the operation.

Ten leads ere used in this two-step test in order to demonstr te that the most dramatic changes are usually observed Leads V and V Therefore, we believ that Leads II V V nd V are all that are required after the two-step test

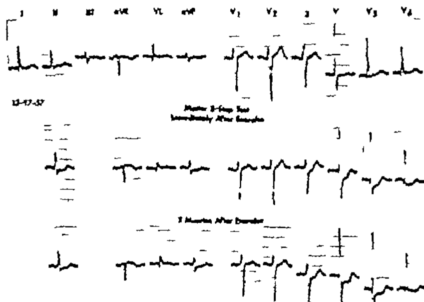


Fig 8 R V 45- ear-old man with severe angina pectoris as practically in tatus anginosus He was, therefore given iproniazid He lost all his pain H became completely as mptomatic no matter what physical or mental stress occurred I fact, he felt so well ith the iproniazid that he ov erdid

The resting ECG taken on Dec 17 1957 was normal (op row).

The two-step test performed 7 eeks af er the complet relief of pain with iproniazid as just as dramatically positiv as it had alr been I other ords the drug eliminated the heart pain, but he coronary artery dise se as unchanged as severe as before

The exercise tracings show 10 leads the most prominent changes are in V and V as usual

The two-step test an be used in ph siological and pharmacological investigations

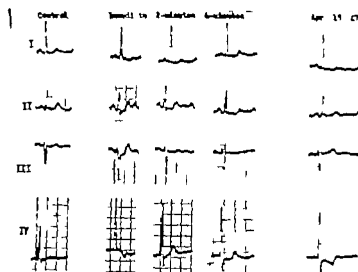


Fig. 9. E. W., a 52-year-old woman, had had angina pectoris for 1 year, hypertension for 10 years, and diabetes for 6 years.

The resting ECG was normal. Only Leads I, II, III, and V are shown.

The two-step test on April 11, 1946, disclosed RS-T segment depressions of the ischemic type and T-wave inversions.

On April 15, 1947, while the ECG was being taken, the patient suffered a spontaneous attack of angina. This tracing reveals changes very similar to those following the two-step test. In the main, the ECG taken after exercise and the tracing recorded during an episode of angina are similar, as would be expected.

On April 19, 1947, 4 days later, the patient developed status anginosus and died. There was evidence of transmural myocardial infarction.

that we have performed, we have seen only one instance in which myocardial ischemia appeared. In this case an over-enthusiastic Fellow in Cardiology kept the patient walking even after pain occurred. Fortunately, the ECG returned to normal within a few hours. The other case was brought to our attention by a physician who did not appreciate that his patient was in the premonitory phase of infarction; this man developed subendocardial infarction within 24 hours of the test.

When the control or resting ECG is abnormal but stable, the two-step test can be performed with complete safety. A most important use of the test, and need for it, is in the evaluation of the function of the heart following myocardial infarction. A total functional recovery does often take place and a negative double two-step test suggests that this has happened (Fig. 15). On the other hand, the appearance of an ischemic S-T segment or a further deepening of an underlying ischemic depression in the resting ECG signifies that active ischemia is still the result of moderate exertion and that the coronary circulation is below par (Figs. 14, 20, and 23).

Procedure

The technique of performing the Master two-step test is described below. In the evolution of the test, different heights of steps from 6 inches to 12 inches were first tried. Everyone walks, no matter how sedentary he has become, no matter how often he uses the automobile. We soon found that the tall man had a mechanical advantage when the step was more than 9 inches in height, and that steps only 6 or 7 inches high were very uncomfortable for all. By 1929 we had learned that steps exactly 9 inches (23 cm.) high were best, no matter what the height of the man or woman. The depth of the steps should be sufficient for a man's foot, and 9 to 10 inches (23 to 25 cm.) is an approximate measurement. The steps should be wide enough for walking; if they are too narrow, this makes for insecurity. Steps wider than 18 inches (46 cm.), preferably at least 22 inches (56 cm.), are ideal (Fig. 1).

The steps should be of solid wood and

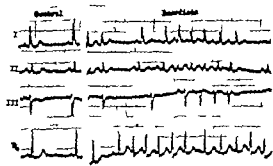


Fig. 10 B. W. 65-year-old man had classical angina pectoris. For 4 years he had also complained of "rapid palpitation" of the heart.

Results of a resting 12 lead ECG and chest x-ray were entirely normal. Only four leads are shown: I, II, III, and V.

The two-step test revealed transient paroxysmal auricular fibrillation immediately after exercise.

The paroxysmal auricular fibrillation was thus found to be the cause of the patient's palpitation. For discovery of arrhythmias it may be helpful to obtain the "immediate" tracing as quickly as possible. Monitoring the test during exercise may also be of assistance.

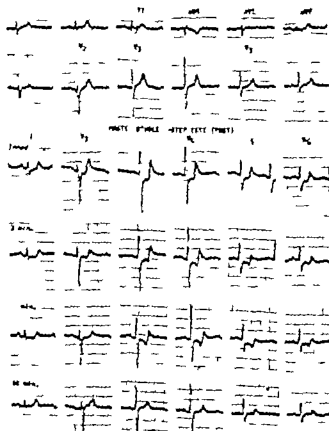


Fig. 11 I. M. G., 46-year-old man, had a severe anginal syndrome.

The resting ECG showed Q waves in Leads V and V, which suggested an old anteroseptal wall infarction of the left ventricle. The postexercise tracing disclosed dramatic "ischemic" RS-T depressions, and the T wave became completely inverted in V-V. There was slight U-wave inversion in V-V. (From Dis. Chest 51:347, 1967).

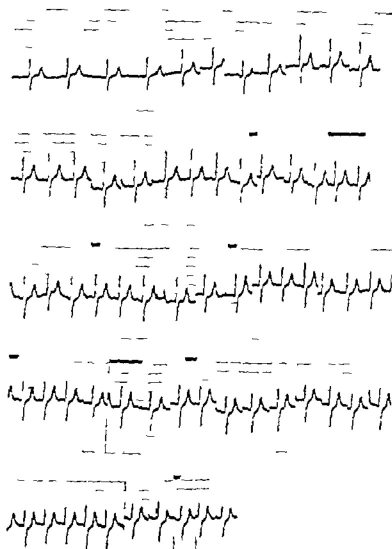


Fig 11B Same patient in Fig. *11A* The monitored test revealed J depressions of the RS-T segment which gradually increased in depth to almost 3 mm near the end that is, on trips 37 to 40 J depressions of this depth are always abnormal. The appearance of these only at the last few *trips illustrates* the necessity of performing the full test—that is, the *standardized* number of trips (From Dis. Chest *51*:347 1967).

above all firm They should not move as the patient walks. The floor should be level and the steps should be placed about 10 inches from a wall. This lends a feeling of security to the patient. If he is elderly or if for some other reason he is unsteady he can put his hand out and touch the wall for support. On the other side will be the physician nurse technician or whoever is supervising the test who will give the patient support if need be by firmly grasping the arm and helping the patient to traverse the steps. Of course the patient must not be lifted vertically because then the work he performs per minute is decreased

To prevent the steps from slipping we have nailed a thin rubber mat on the top of each step and also on the bottom of the steps to make complete contact with the floor This helps if the latter is slippery

The question has always arisen whether the patient should partake of food before performing the two-step test. We have made it a rule to omit breakfast entirely or permit only a light one. If the test is

to be made in the afternoon two hours after lunch would be sufficient or again, any time after a very light lunch. A heavy meal would make a difference in the test. The patient should not smoke (In fact some investigators have used smoking as a test William Dock for example feels that the ECG after smoking is a test for coronary insufficiency)

We like to maintain conditions as basal as possible, but the atmosphere should not be too quiet nor should the room be noisy with people constantly passing by the door telephones ringing and loud talking An ordinary tranquil atmosphere is preferable

We have the patient come without any drugs Of course the test should not be performed if he has had digitalis quinidine, or other drugs that may affect the ECG

Perhaps the most important principle in the technique of performing the test is to make certain that the patient is not in the throes of an impending infarction. Therefore a history should be taken before the test is performed If there has been history of severe pain within the last week or two even if the ECG is still normal the test should be deferred. If there has been a sudden change in the characteristics of the pain—for example increase in severity a new location more easily triggered pain pain that requires much more nitroglycerin—all this again suggests an impending infarction, and the test should not be performed at that time even though the ECG is normal. However the test is not dangerous, since it is always emphasized to the patient that when he experiences pain pressure or any other type of chest sensation in the chest arm or neck, he must stop immediately This emphasis is made because, rarely the patient will insist on continuing the test even after he has suffered pain (he wants to make sure that he is doing sufficient work) This type of event must be avoided

The age sex, and weight of the patient determine the number of trips to be performed as indicated on the published chart (Table I) During the exercise the limb electrodes are left in place with the lead wires attached. The subject holding the chest electrode and his cable ascends to the top of the two steps and walks down the other side (Fig 1) This is counted as one trip He then turns around and retraces his steps (the second trip) and so on until the full number of trips is completed in three minutes. He should always turn toward the physician nurse or technician since in so doing he reverses the direction of turn at the end of each trip and "unwinds" himself avoiding dizziness. The turning also provides a rest (Thus there is a decided difference between walking steadily up 72 steps each 9 inches high and performing 36 trips on the two-step apparatus and pausing after each crossing

The rate of ascent and descent should be controlled A variation of from one to three seconds in the duration of the test is permissible A large electric clock with a sweep second hand should be hung on a wall within constant and full view of the physician nurse or technician who is supervising the test Even better is a stop watch which registers the minutes as well as the seconds. (A metronome although not essential is helpful in maintaining a constant rate We have used a specially devised metronome* which is set to click with each step the patient ascends or descends. At the end of a single trip, the instrument clicks twice to signal the time to turn around The timing is easily adjusted for any number of trips indicated by the chart)

Either the physician performs the test himself or if a competent nurse or technician does it, he stays close by (Non medical people must be thoroughly trained but in any case the physician will have first evaluated the condition of the patient by taking his history)

When the exercise has been completed the patient lies down immediately he is encouraged to relax fully and the lead wire cable is instantly inserted into the machine. Electrodes and connections should be checked very quickly to make certain that they have not been disturbed during the test. Tracings are recorded immediately after exercise in two minutes and finally in six minutes In fact, they are repeated until the record returns to the

*Manufactured by Electronics for Medicine, White Plains, N Y

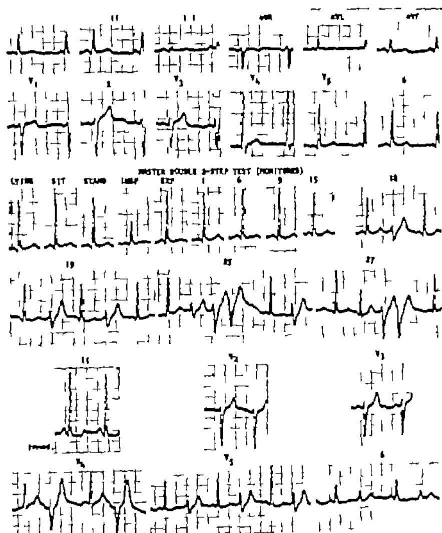


Fig. 14-A B Z., a 62-year-old man had had effort angina for 2 years. The chest pressure had become orse nd recently had occurred spontaneously
The resting ECG (pper tw rows) was within normal limits.
The monitored double two-step test showed fusion entricular premature contractions (VPC) at trips 18 and 19 On trip 25 there were three consecutive VPC the first contraction was fusion beat. On trip 27 chest pressure appeared and the exercise was terminated

resting or control appearance. Leads taken are V_4, V_5, V_6, V_2, and II usually in that order and in a manner to be described under the technique of "monitoring (Figs. 7 8 and 20)

Occasionally after exercise the stylus of the ECG may wander especially if respiration is rapid or deep whereas correct interpretation of the RS-T segment can be made only in a baseline that has remained level for at least three consecutive beats. If the patient briefly suspends respiration the ECG is less apt to wander The P Q or P R interval (and not the T P interval) is the reference point with which the level of the RS-T is compared.

Technique of monitoring The ECG may be recorded while the patient is actually performing the two-step test (Fig 1) A direct hook up system requires no electronic equipment the subject remaining connected to the ordinary ECG machine by the patient cable. The key to successful monitoring is found in the special electrodes and the technique of their application. We use a commercially available

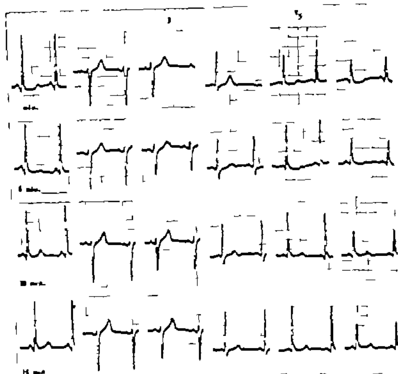


Fig. *12B* Same patient as in Fig 12A The post-exercise ECG revealed bigeminy due to VPC in the "immediate leads V_4, V and V tracings. There were ischemic RS-T segment changes, for example, in the immediate Lead II

Arrhythmias often occur only in the tracing made immediately after exercise.

product, which resembles a Band aid has a central 3/8 in diameter steel mesh for electrode jelly and is disposable. Adapters connect to snap-fasteners on these electrodes and to lead wires of the ECG One of these special electrodes is placed in the regular Lead V position for monitoring this V lead. The other special electrodes are placed on the distal end of each clavicle (these are the connections for the right and left arms) and finally an electrode is placed under the last rib in line with V_4, or on the iliac crest (this is the left leg connection)

The immediate" tracing following the exercise may be very important that is why we keep on recording the ECG even during the few seconds required for the patient to lie down quickly after the test. Moreover the maximum heart rate after exercise is thus obtained.

Criteria

The most controversial problem in the two-step test has been the criteria for positivity of the test. Practically everyone agrees that an *ischemic depression* (Fig 4 B) is an abnormal one but some disagreement exists concerning the amount of depression necessary to make it so. By ischemic is meant a completely horizontal depression of the ST segment or actually a downward-sag contour It was Paul Wood who first called this change ischemic In our previous papers we made numerous references to this type of depression and we have presented many actual case illustrations. Many more are shown in this paper

The majority of investigators require an "ischemic depression of 1 mm or more before they call the test positive. In general this is correct, but because we have seen ischemic depressions of ½ mm (Figs. 6 and 13) or between ½ mm. and 1 mm proved to be abnormal by follow up we would advise the reader to consider a depression of more than ½ mm abnormal until it is proved otherwise. At least it should be kept in mind. Furthermore it is

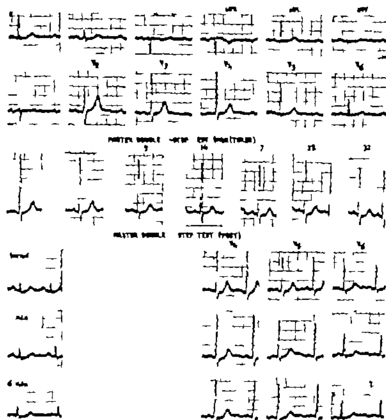


Fig. 13. L. H., 67-year-old male physician, with an anginal syndrome, showed findings similar to those of the preceding case.

The resting ECG was negat (upper two rows).

The monitored two-step test revealed benign depressions of the RS-T segment on trip 3 which became abnormal on trip 17 and still more so on trip 32. However, it did remain type; no ischemic depression of the RS-T segment was observed.

The post-exercise ECG disclosed ischemic ST depression of only ½ mm. in the 2 minute Lead V tracing. Although this was borderline, in conjunction with the anginal syndrome, it was considered an abnormal response to exercise. This opinion was substantiated a year later when the patient developed myocardial infarction.

Again, the depth of the ST depression correlates with the severity of the coronary disease only in a general way. Occasionally an ischemic depression of only ½ mm. may be important. In other words, the ECG findings should be correlated with the clinical. Contrariwise, dramatic RS-T segment depressions after the two-step test are often compatible with long life even if the patient has a severe anginal syndrome (see Fig. 14). (From Dis. Chest 51:347, 1967.)

to be recalled that we have repeated time and again that the two-step test should be interpreted only in association with all the clinical findings. In private practice this is not difficult, but it may be a problem for the Insurance Medical Director or for the responsible physician in the military force when an officer is being examined for promotion or on an annual basis. The same difficulty is encountered when an airplane pilot is examined. In these and similar situations, because of the intense ambitions of these candidates, all of the facts in the story may not be elicited.

When an ischemic depression of only ½ or ¾ mm. appears after the two-step test and the history is not classical or suggestive, then the referring doctor and the patient should be reassured and told that there are some equivocal changes in the postexercise tracing, and that it would be well for the patient to avoid strenuous physical or mental stress until he returns in six months or a year for a repeat evaluation of his status.

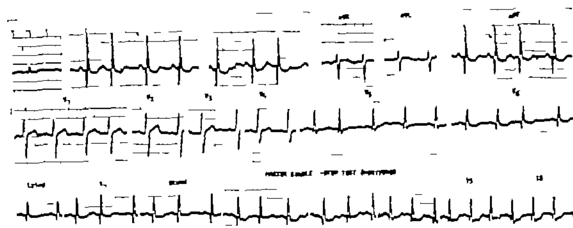


Fig. 14A. M. N. man now 80 years of age had suffered a coronary occlusion in 1931. The ECG at rest (upper row) still shows the effects of this transmural infarction: there are Q waves in Leads II, III, and V. There are also RS-T segment depressions and T-wave inversions in these leads. Auricular premature contractions are evident in Leads II and III. The ECG has remained the same on scores and scores of examinations.
The patient, then, has had a severe anginal syndrome for 36 years. Unless he takes nitroglycerin prophylactically, he cannot walk more than a city block (From Dis. Chest 51 347 1967).

Our criteria have been confirmed in our recent papers by a study of those who possess unequivocal coronary disease (Figs. 7 to 14). Thus, we selected 200 patients with classical angina, 100 of whom had normal resting ECG's and 100 who had abnormal but stable tracings. The statements of positive criteria we have just described were corroborated by a review of these 200 patients, a few of whom were in status anginosus (Figs. 7 and 8), and also on the basis of our large experience.

We have also recorded that *elevations of the RS-T segment* above those seen in the resting ECG are also an ischemic or positive response. This is often seen in patients whose stable resting tracings are abnormal (Fig. 23). They often have Q waves already and when they do, it is in those leads usually that further RS-T elevation appears. Thus, this elevation will often be seen in patients with ventricular aneurysm. The elevations already present in the resting tracing become elevated further. In our opinion this constitutes an abnormal test and indicates active coronary artery disease even if the patient is completely asymptomatic.

The transient appearance of a Q wave not present in the resting ECG constitutes an abnormal result (Fig. 21).

The appearance of a left bundle branch block also indicates an abnormal test.

Similarly, the transient appearance of an inverted U wave constitutes an abnormal test (Figs. 11 and 16).

A serious arrhythmia may also be considered an abnormal response (Figs. 10, 12, 21B, and 23). Thus, a very transient ventricular tachycardia may be seen—although very, very rarely. The same holds true for complete or partial heart block with dropped beats. Slightly more frequent are atrial tachycardia and fibrillation and much more frequent are multifocal ventricular premature contractions or three or four successive premature ventricular contractions. These are accepted as an abnormal response to the two-step test. Never has a sustained or permanent disturbance of rhythm been witnessed. Another point of interest is that these arrhythmias have been usually known to occur occasionally in these patients. In the rare instance in which they have not been recognized before, the appearance of the dysrhythmias often explained such symptoms as palpitation, rapid heartbeat, light headedness, dizziness, feelings of faintness, and even actual syncope (Fig. 10).

A good deal of doubt exists concerning the significance of T wave inversions. We do not refer to small T waves, or slight inversions of the T waves; these are not significant. However, if an upright "T"

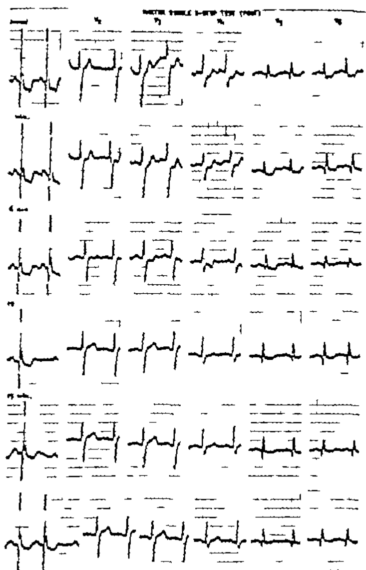


Fig. *14B*. Same patient as in Fig. 14A. The single two-step test monitored showed RS-T depressions which became deeper and deeper as the patient walked. Auricular premature contractions were also observed.

Even though only a single two-step test was performed the ECG disclosed distinct RS-T segment depressions and it required 20 minutes before the tracing returned to the resting state.

This case demonstrates that even dramatic ST depressions may be compatible with long life. (From *Dis. Chest* 51:347, 1967).

wave of at least 1½ mm becomes inverted to at least the same amount that is a positive test. Similarly, if an inverted T wave present in the resting ECG becomes transiently positive to at least 1½ mm it is a positive test (Figs. 9, 11, and 23).

In all these instances, namely, of RS-T elevation beyond that seen in a control ECG, appearance of a transient Q wave, of left bundle branch block, of widening of a QRS, of serious arrhythmias, of a "U" wave inversion, or of a change in the T wave such as described—these changes will be accompanied by "ischemic" depressions of the RS-T segment. So, for all intents and purposes, the "ischemic" type of RS-T depression still remains the test criterion of an abnormal response to the two-step test. Only on one or two occasions among hundreds of tests have we seen, for example, such a situation as this: an upright T became deeply inverted after

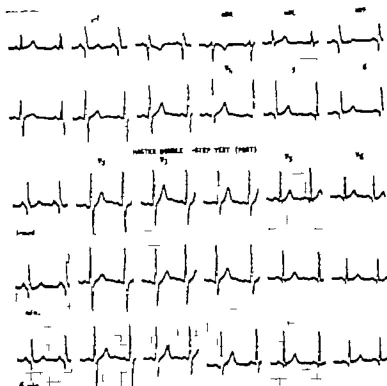


Fig. 15A. In contrast to the case shown in Fig. 14, in which there was persistent angina pectoris and an abnormal two-step test following coronary occlusion for nearly 36 years, this is the report of a young doctor, J. L., who developed transmural infarction at the age of 31 and whose exercise test became normal in a short time.

The first two rows show the resting ECG. Again there are present Q waves in Leads II, III, and aV with T-wave inversions in Lead III (From Dis. Chest 51:347, 1967).

the two-step test, this was the sole change, and it was proved by follow up to be significant and yet an ischemic depression was absent. In one man with hypertensive heart disease there was seen an isolated transient Q wave together with a significant change in T wave polarity without concomitant RS-T depression.

The very sick man, the one with dramatic RS-T segment depressions in the two-step test, is the man whose post exercise tracings will require 10 to 20 minutes to return to the resting record rather than the usual 6 minutes (Figs. 14 and 21).

We believe that the vast majority of investigators will go along with the foregoing indications of what constitutes a positive two-step test. A good deal of argument has been engendered in the interpretation of the "j" type of RS-T segment depression. This is a depression beginning at the end of the QRS or junction of this point with the T wave. The ECG never is completely horizontal; it may rise rapidly (Fig. 3) or very slowly to the T wave (Fig. 4, A). In fact, it may rise so slowly that it is practically horizontal, that is, near ischemic (Figs. 4, A and 16 to 19). We have described quantitative measurements for more precise interpretation of this "j" type of RS-T depression, but we now feel that if one observes visually a "j" depression which is near ischemic, it should be considered a positive result. Others never consider any "j" depression positive, but here we strongly disagree. We repeat, we feel that *if it is a near ischemic, it has a definite significance.* We have had a good deal of indirect proof of this. Very often one will observe a "j" type in one lead with ischemic depression in other leads. However, the clinical findings and follow-up

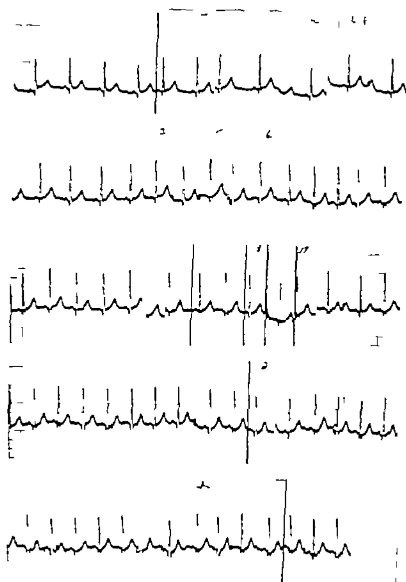


Fig 15B Same patient as in Fig 15 A Th regular double t o-step test was completely negati e. This correlates well w th the linical stor The patient has apparently made a complete recovery It is now 6 years since his heart ttack and he has lost ll pain. At first he was ery caref l, but confidence returned with the passage of time and he has become careless—he works very hard often around the clock (From Dis. Chest 51:347 1967).

investigations have confirmed this inter pretation. If the j rises rapidly we con sider it a ben gn change (Fig 3)

Again the j type of RS-T depression we described as near ischemic will have the QX/QT prolonged that is, the time it takes to return to the baseline namely QX divided by the time of entire ven tricular systole QT will be 50 per cent or more Another measurement we use too is the prolongation of the QT ratio (or QTr) If the actual QT measurement over that which it should ideally be for the same heart rate is increased to a ratio of more than 1 07 this may be abnormal If both the QX/QT and the QT ratio are increased then we interpret the "j as abnormal. However we ourselves now do not bother with the measurement al though by use of the QT Calculator of the Bowen Company in Bethesda Md one can quickly perform these calculations. We now advise visual inspection we re peat if the RS-T segment is "near" is-

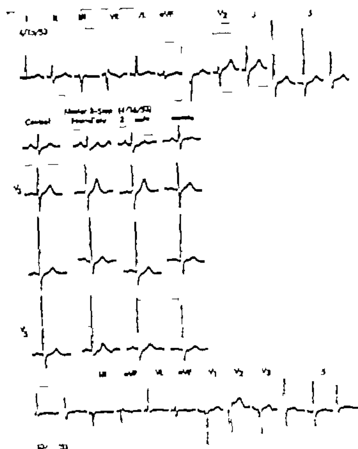


Fig. *16.* J. M., 54-year-old man, had an anginal syndrome.

The resting ECG was essentially negative, although the voltage in the chest leads was high.

The two-step test showed a significant j type of RS-T segment depression in the immediate lead V and V. There were inverted "U waves in the "immediate V₆. The fact that these changes were significant was substantiated by the record made on Oct. 15, 1963, just six months later. The patient had sustained a transmural myocardial infarction affecting the anteroseptal wall of the left ventricle, as indicated by the QS in V-V₄.

chemic it is abnormal, whereas if the j rises rapidly to the baseline, it is innocuous.

There is some controversy, too, in regard to the respective values of the monitored test versus the regular postexercise two-step test. We have found the latter much more valuable than the monitored (Figs. 19 and 23); however, the monitored lends itself to research, for example, study of heart rate.

It will be recalled that one of the most important safety factors in performing the two-step test is to have the patient stop the very instant *pain or pressure* appears in the chest, arm, between the shoulder blades, or other related areas. In the vast majority of patients the ECG will be abnormal when this occurs (Fig. 9). In a very occasional case this does not happen. Let us say the table called for 36 trips for the age, sex, and weight of the patient, that pain occurred on trip 22, and that there were no changes in the postexercise ECG. On repetition of the test an hour later or the next day, if the patient walks even a little farther, takes a few more trips than the 22 (for example 26 or 28) or if he now can perform the entire number of trips, the ECG will be abnormal. We explain the foregoing in this way. The patient on being questioned will say that he experienced only the slightest pressure and that he stopped because he knew that if he continued he would develop pain.

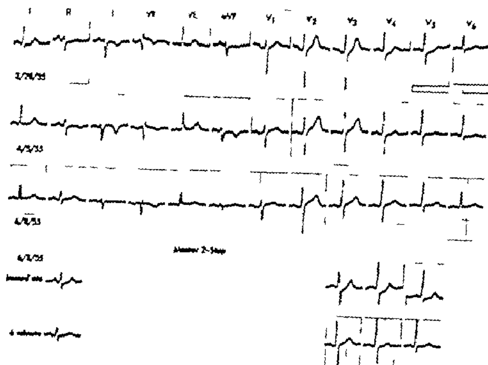


Fig. 17. H. T., a 63-year-old man, had an attack of subendocardial infarction. This is revealed in the first three ECG's. These had returned to normal by June 8, 1955, but the patient continued to have a classical anginal syndrome.

A double two-step test gave positive results. There were only abnormal RS-T segment depressions. The patient died about 2 months later. This, then, is an illustration that slowly rising are observed in patients with severe coronary disease as well as ischemic RS-T depressions.

It would appear that the brain is alerted before the myocardium actually becomes ischemic and so the postexercise ECG remains negative. The mind knows that if the patient were to continue real pain or pressure would appear. We have termed this concept *impending angina*.

How often does pain appear in the two-step test. We have found that it transpires in about one fifth of the patients with coronary artery disease and we refer to any type of discomfort in the chest or arms, either during the test or when the patient lies down quickly after completion of the exercise to have the postexercise tracing recorded. Of course the walk is stopped the instant the pain or pressure occurs. More often the complaint appears when the patient lies down in the horizontal position. It disappears almost immediately if it does not the patient is asked to sit up. It is very rare indeed that he requests or accepts a nitroglycerin tablet since the discomfort is slight.

For years we insisted that the resting ECG be normal before the two-step test be essayed. However for the last five or six years we have not hesitated to perform the two-step test on patients who have *abnormal resting but stable ECG's*. Thus a patient who has recovered from a myocardial infarction may have an electrocardiogram with Q waves and with the T waves inverted and this will remain unchanged for years. As a matter of fact the patient may have even become completely asymptomatic. Whether this type of patient is asymptomatic or not we do not hesitate to perform the double two-step test again—of course with the usual admonition that he stop if pain or pressure appears.

We feel that the two-step test is very helpful in myocardial infarction. Although we have not completed our follow up we have studied a fairly large number already we feel that a positive two-step test correlates with a distinct anginal syndrome

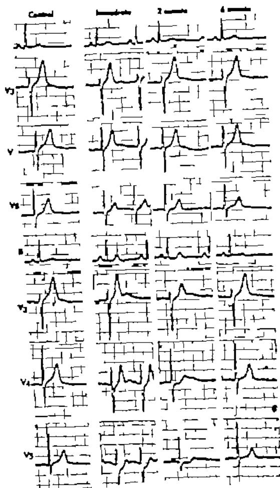


Fig. 18. P. V., 49-year-old man, had severe angina pectoris.

The resting ECG was normal.

Since the patient was in status anginosus, it was thought safer to do only a single two-step test. It was negative. Therefore the regular double two-step test was performed the next day. "Ischemic" RS-T changes appeared, particularly evident in the 2 minute Leads V_4-V_6. The "immediate" Lead V revealed an abnormal J depression, more than 3 mm. deep.

The patient developed a severe myocardial infarction 2 months later and died.

Often, even in a severe anginal syndrome the single test will be negative and the regular double two-step test must be performed before changes appear, which offers support to our contention that a standardized number of trips should be employed for the exercise.

with an enlarged heart, with the presence or history of heart failure, or other evidence of interference of coronary circulation or definite myocardial involvement (Figs. 14, 20, and 23). On the other hand we are of the opinion that when the two-step test shows no change from the abnormal resting ECG, no matter how abnormal, in all probability the patient has made a good functional recovery (Fig. 15). Of course, if the resting ECG is normal and the double two-step test is also negative, it is excellent evidence that there is no interference with the coronary circulation or with the myocardial function (Fig. 2).

The two-step test and silent coronary disease

By silent coronary artery disease we mean completely asymptomatic disease; anginal equivalents and other symptoms of heart disease, such as dyspnea, palpitation, and weakness, are excluded. This entity has been demonstrated by epidemiological survey and by pathologists who have discovered myocardial infarctions at postmortem examination and then retrospectively ascertained that the patient never had a complaint, never was sick, never lost a day in his work because of illness. This silent form of disease has been further substantiated in reports on "sudden deaths" by medical examiners. It is observed daily by physicians during routine examination of their patients, on surveys of executives, by the military medical corps even in apparently healthy men in the armed forces, and by the industrial physician. What has not been realized, is the *vast extent* of asymptomatic coronary disease. In previous reports, my colleagues and I estimated that 4 to 6 per cent of the population of 35 or more years of age has silent significant coronary disease without infarction, and that approximately 800,000 men have silent acute myocardial infarctions yearly.

In my own private practice, every week I see almost a score of the type of case that has just been described. The patient is referred because routine ECG's showed unexpected but definite abnormalities. Even evidence of previous transmural myocardial infarction in the tracing is discovered—for example, Q waves and QS patterns. With a normal resting ECG an abnormal two-step test may have been observed, the patient would then have been referred for consultation because he had no complaints.

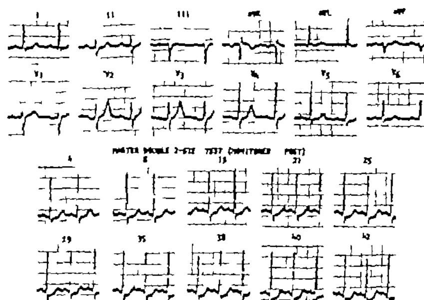


Fig 19 A J F is a man with classical angina pectoris
The upper tw row show the resting ECG which is essentially negative. There is a left axis deviation with a slight depression of the RS-T segment in Leads V and V₆. It has been this way for years.
The monitored two-step test show significant j type of RS-T segment depression, except perhaps in the last trip (42) Here there are short but distinct "ischemic RS-T segment depressions (From Dis. Chest 51:347 1967)

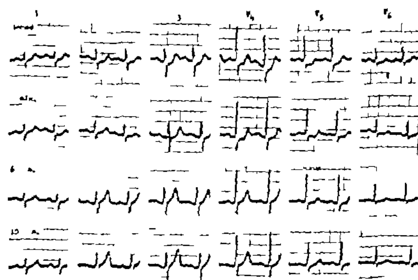


Fig 19B Same patient as in Fig 19 1 1 the postexercise ECGs there are "ischemic depressions of the RS-T segment maximal in the 2 minute Lead V₆.
The results reveal the necessity of standardization of the t o-step test. It was essential for the patient t walk the full number of trips in the published table. Only on the last few trips did the ECG become positive (From Dis. Chest 51:347 1967).



Fig. 20. N S 63-year-old man, had had previous coronary artery occlusion. The patient was first seen i 1935 when he presented himself with the classical anginal syndrome. However he was free of symptoms for the following 11 years no matter what he did.

The patient has been examined regularly every 6 months. The resting ECG always showed Q waves in Leads II III and V the remains of the old coronary occlusion. It was essentially negative. The two-step test was always positive.

I the beginning of 1967 classical syndrome reappeared

Ten leads are shown in the two-step test to illustrate the point that the most marked electrocardiographic changes are usually observed in Leads II V V V or Leads II V V_5, and V The case is also presented as one of completely asymptomatic but significant coronary disease for 11 years Nevertheless, the two-step test demonstrated active coronary artery disease

Many examples of silent coronary artery disease have been cited. Thus, it has been observed for years that a patient may lose his anginal syndrome after an acute myocardial infarction. Again without the intervention of myocardial infarction an angina may suddenly become completely silent after a long history of chest pressure or pain. Yet in both instances active coronary disease may still be present. The classical angina may then return without any obvious precipitating cause.

It must now be apparent that silent and often severe coronary disease exists in many diverse forms. The point is that the two-step test will demonstrate it whether or not the control ECG is negative, or abnormal but stable.

Two examples of asymptomatic coronary disease follow

N. S. was 71 years old i 1967 H first presented himself in 1935 with classical anginal syndrome. After one yea observation, that is in January 1936 he lost all his symptoms This remained the situation for the years following H presented no complaint whatsoever no matter what he did, no matter how hard he worked I fact,

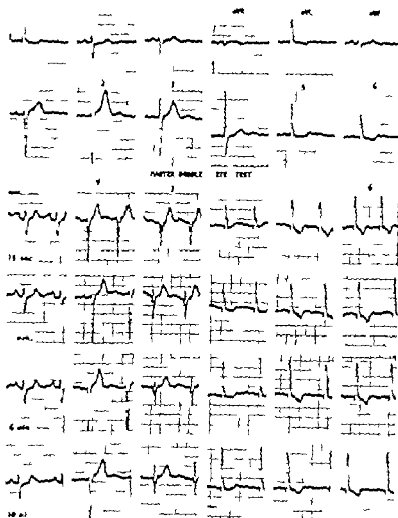


Fig. 21. S. F. 68-year-old physician with long-standing hypertensive heart disease and an enlarged heart, was observed for 31 years, almost entirely because of his severe hypertension. He had an anginal syndrome at first. This disappeared completely for years and finally returned about years before his death.
The resting ECG showed the pattern of left ventricular hypertrophy or even left ventricular strain, i.e., distinct left axis deviation, ST depressions, and T wave inversions. However, it remained stable for years.

overconfident and on occasions he would rush about, hurry up a hill against the wind, carry a heavy suitcase, and hasten to the airport or railroad terminal. He never had occasion to use nitroglycerin during all these years. At the beginning of this year, 1967, in winter, he again noticed tightness of the chest on walking up a hill, or against the wind. He obtained immediate relief by nitroglycerin. Yet all symptoms had been completely absent for eleven whole years.

In all this interval of silent coronary disease, that is, 1956 through 1966 inclusive, the ECG at rest had been normal, but the two-step test had disclosed dramatically ischemic changes in the RS-T segment. In fact, it required 20 to 25 minutes for the tracing to return to the same state as the negative resting ECG. This was always the case during numerous regular 6 month check-up examinations (Fig. 20).

W. R. was referred to me on Nov. 26, 1956, at the age of 56 years for moderately high blood pressure. This had been discovered on a routine examination by the family doctor. The patient had had no complaint whatsoever. He was placed on antihypertension therapy and for years the blood pressure was maintained at about 150/90 mm. Hg. At times, however, the systolic pressure was 200 mm. Hg or more and the diastolic 110 to 120 mm. Hg.

Teleoroentgenogram and fluoroscopy always disclosed clear lungs, normal heart, and tortuous and dense aorta.

The resting ECG was abnormal but always stable. There were RS-T depressions and T wave inversions in Leads I, II, III, V_5, V_6, and V_7 (Fig. 22).

Since the double two-step test was always abnormal and required more than the usual six minutes to return to the resting state, a single test was usually performed. This test was performed last

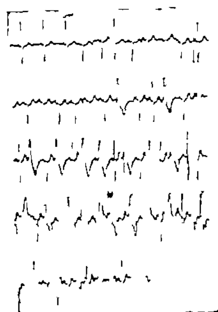


Fig. 21B. Same patient as in Fig. 21A. In the monitored tracing, ST changes appeared; they increased in depth as the exercise continued. Ventricular premature contractions were present at trip 7, formed bigeminy at trip 10, and were multifocal at trip 21. Postexercise ECG revealed no arrhythmia. Transitory Q waves appeared in Leads V and V and "ischemic, sagging ST depressions in V. The tracings had not returned to the control state even 10 minutes after exercise. The longer the time required to return to the pre-exercise record, usually the sicker the patient.

on April 14, 1966, and showed ischemic RS-T changes in Lead V (Fig. 22).

During the patient's 6 month examinations from 1956 to 1964 he never suffered a single complaint. He worked for a telephone company as foreman of linesmen. Often he went out in storms to supervise repair of downed telephone poles and wires. Indeed, on rare occasions he worked very hard, although ordinarily he led a sensible existence.

When last seen, on April 14, 1964, his physical examination was entirely negative except for a blood pressure of 150/106 mm. Hg. The single two-step has already been described. It was abnormal (Fig. 22). On June 14, 1964, the patient developed severe chest pain. He was rushed to the hospital and died within a few hours.

It is thus seen that the two-step test is of real value in the discovery of silent coronary artery disease (Figs. 8 and 20 to 23). The ECG is the best means of establishing the presence of coronary disease in the presence or absence of symptoms, but as we have reiterated for years, it must never be assumed that, because the resting ECG is normal, coronary disease is absent. The two-step test or an equivalent exercise test must be done before excluding it.

Summary

There is a genuine need for the two-step test. In the diagnosis of coronary artery disease the history is not always helpful; it may be atypical. Moreover, the condition may be completely asymptomatic. Physical examination is rarely revealing. The resting ECG is indeed helpful if abnormal, but a negative tracing does not exclude coronary disease. The ECG is normal in the majority of cases of angina pectoris.

In the United States of America alone there are probably 600 000 deaths annually from coronary disease, pointing up the value of the two-step test and affirming its importance in completely asymptomatic disease.

The physical background of the patient is unimportant. If he suffers from ischemic heart disease, the two-step test will be positive whether he has always been an athlete, a prize-fighter, or a sedentary man.

A test for coronary disease must be standardized, for the response to exercise varies with the age, weight, and sex of the individual. If the standardized test is used the results are comparable anywhere in the world. Physiological and pharmacological studies on human beings are possible.

Evidence that the two-step test should be standardized is gathered from the monitoring of our patients with significant coronary artery disease. In almost half the patients it is necessary to perform the full number of trips before the test becomes positive. Too little exertion is often insufficient to make the test abnormal; however, there is overwhelming evidence that even normal people, if exercised to excess, may show ischemic RS-T depressions.

When the standardized table is used, the test will be found to be completely safe. It must never be performed when an impending infarction is suspected. Furthermore the patient must be admonished to stop immediately the instant he de-



Fig. 22. W. R., 64-year-old man, had hypertension and an enlarged heart. The resting ECG (upper two rows) disclosed a left ventricular strain pattern. The patient was completely asymptomatic and had been referred for consultation in 1956 only because of hypertension.

The resting ECG was abnormal but always stable. There were RS-T depressions and T wave inversions in Leads I, II, III, V, V and V.

Since the regular double two-step test was always abnormal and required more than the usual 6 minutes to return to the resting state, a single test was performed on April 14, 1966. It revealed "ischemic" RS-T depressions in Lead V_4.

During his regular semiannual examinations from 1956 to 1964 the patient never had a single complaint, although he worked hard as a lineman for the telephone company. On June 14, 1964, he developed severe chest pain and died within a few hours.

velops discomfort, pressure, or pain in the chest or arms.

Procedure. In regard to the procedure, conditions are maintained as basal as possible; the atmosphere should be neither too quiet nor too noisy. The patient should appear at the office without having taken any drugs that day. The age, sex, and weight of each patient determine the number of trips to be performed, as indicated on the published table.

The rate of ascent and descent should be controlled by the sweep second hand of a timepiece. A physician either performs the test himself or remains close by if a competent nurse or technician does it.

Leads taken are V_4, V_6, V_6, and II, or V, V_5, V_6, V_3, and II, usually in that order.

The ECG may be monitored, that is, recorded while the patient is actually performing the test. The immediate tracing following the exercise may prove valuable if it is recorded even during the few seconds required for the patient to lie down quickly after exertion (the maximum postexercise heart rate is thus obtained).

Criteria. With regard to criteria, an

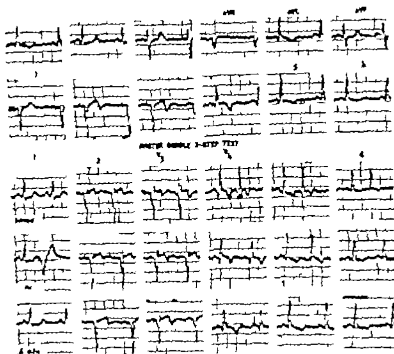


Fig. 23.1 S. Y. now 75 years of age developed a coronary occlusion in 1957. He has been completely asymptomatic ever since. This is another example of silent coronary artery disease.
The resting ECG still showed evidence of an old anterior wall infarction, particularly in the chest leads.

ischemic depression of the RS-T segment denotes an abnormal condition. Disagreement exists only concerning the amount of depression. Most investigators require a depression of 1 mm or more for a positive test. This is true in general but many times we have seen depressions of $\frac{1}{2}$ mm and certainly between $\frac{1}{2}$ and 1 mm prove to be definitely abnormal. We therefore consider a depression of more than $\frac{1}{2}$ mm a positive test. Finally, the two-step test should be interpreted only in conjunction with all the clinical findings. Our criteria have been confirmed by a study of those who possess unequivocal coronary disease, i.e., classical angina.

Elevations of the RS-T segment above those seen in the resting ECG, transient appearance of a Q wave or a left bundle branch block, an inverted U wave, a definite quantitative change in the polarity of the T wave, and a serious arrhythmia are all abnormal. However, in practically all these instances, these changes will be accompanied by ischemic RS-T depressions.

Controversy exists in the interpretation of the J type of RS-T segment depression. If it is a near ischemic in contour it is abnormal.

In the vast majority of patients the ECG will be abnormal when pain or pressure appears in the chest, in the arm, between the shoulder blades, or the like. In a very occasional case this does not happen (the patient stops before actual pain appears for he knows that were he to continue the exercise he would develop it); we have termed this impending angina. Pain or pressure appear in about one fifth of the patients with coronary disease who perform the two-step test, and usually when the patient lies down in the horizontal position after completion of the exercise. Nitroglycerin is very rarely required because the complaint is so slight and ephemeral.

For the last five or six years we have not hesitated to perform the two-step test on patients who have abnormal resting but stable ECG's. The two-step test is very helpful in myocardial infarction. A positive

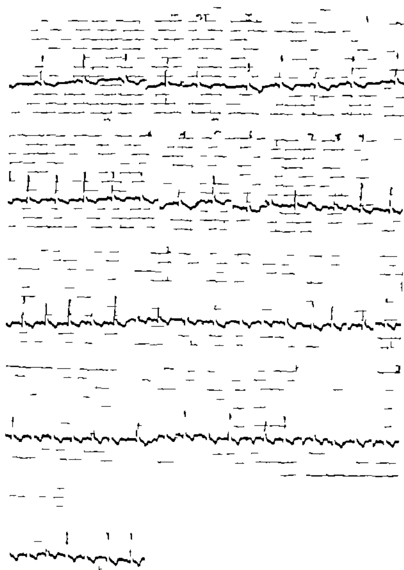


Fig 23B Same patient as in Fig 23A The two-step test revealed no change in the monitored ECG The T wave was inverted at the start and remained so without any RS-T segment depression.

The postexercise ECG disclosed many ventricular and auricular premature contractions. There were "ischemic" elevations and depressions of the RS-T segment In the "immediate" Leads V and V_4. RS-T elevations are observed beyond that in the control tracing RS-T depressions are seen in Lead II There was transient T wave positivity in Lead V_5.

In spite of the abnormal changes in the exercise ECG and in spite of arrhythmias, the patient has been completely asymptomatic for years. He has routine check-up examinations regularly

two-step test correlates with a distinct anginal syndrome with a subsequent heart attack with an enlarged heart with the presence or history of heart failure or other evidence of interference with coronary circulation or of definite myocardial involvement When the two-step test discloses no change from the abnormal resting tracing no matter how abnormal in all probability the patient has made a good functional recovery

The two-step test and silent coronary disease Silent coronary artery disease (completely asymptomatic) is prevalent Examples of this have been cited The ECG is the best means of establishing the

presence of coronary disease but if the resting ECG is normal the two-step test or an equivalent exercise must be done before excluding it.

In conclusion anyone who is responsible for the lives of others, as, for example, bus drivers, train engineers, policemen should have a functional test of the heart. In fact every person in this country 35 years of age or more, should annually receive a physical examination, an x-ray picture of the chest, and an ECG If the latter is negative, the two-step test should be performed.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff Alan F Lyon and Julian Frieden

)

I

Surgical treatment of valvular heart disease

Part I Criteria for operability in rheumatic heart disease

MITRAL VALVE LESIONS

Edmund H Reppert M.D
New York N Y

A total of 20 years has elapsed since the pioneer work of Bailey Harken Bjork, and their associates demonstrated to the medical profession that surgical correction of mitral stenosis is not only feasible but is a necessary adjunct in the therapy of this disease. The last 8 of these 20 years have seen open correction of mitral lesions, either by repair or replacement added to the physician s therapeutic armamentarium. The initial significant, but acceptable risk of surgery has been reduced to an even more palatable level Long term follow up of closed surgery for mitral stenosis shows this therapy to have given significantly superior results to long term medical therapy [1-4] Long term appraisal of open repair or replacement for mitral stenosis and/or insufficiency is obviously not yet possible but results to date are equally promising Indeed few if any informed physicians today would deny that surgery has a place in the therapy of mitral valve disease however there is considerable diversity of opinion as to when operation as well as what type of operation is indicated Unfortunately the diversity varies from the overenthusiastic who would in essence operate upon a murmur to those who finally conclude that medical therapy has no more to offer so we might as well *try* surgery Obviously the criteria for operability lie somewhere between these two extreme and fortunately not too common views. With all the clinical and laboratory data that have been gathered during the past 20 years it should be possible to choose a reasonably optimal time for surgical intervention in the individual patient. The intelligent appraisal of the patient includes correlation of clinical and hemodynamic data and in individual cases must take into account social economic and psychological factors.

Clinical appraisal

Symptoms The pathophysiology of mitral valve disease is such that symptoms result primarily from increase in pulmonary artery pressure or from low cardiac output or both The former is more commonly seen in predominant stenosis and consequently symptoms of dyspnea on exertion orthopnea and hemoptysis are common while fatigue due to low cardiac output is a more common symptom of mitral insufficiency However there is no sharp distinction in symptoms between the two conditions. The presence and degree of symptomatology in the consideration of surgical therapy is most important Except under unusual circumstances no patient without symptoms should be

Associate Professor of Clinical Medicine, Department of Medicine New Y ... of

considered a candidate for surgery. Patients with mild symptomatology which is static, allowing them to carry out their daily activities without difficulty, probably have as good a prognosis with medical management and hence should not be subjected even to the small risk of an operation. However, such patients must be watched carefully as progression of their symptomatology is almost inevitable. When symptoms become progressive and when patients are unable to carry out their daily activities without mild-to-moderate difficulty, an operation is strongly indicated. When symptoms have reached the stage of persistent incapacitation of the patient, the optimal time for surgical intervention has passed. Up to this point surgery, whether open or closed, entails a mortality risk of only 2 to 5 per cent, and the results are most gratifying; after this point of incapacitation is reached, the surgical risk approaches 15 to 20 per cent and the results, although much better than can be anticipated from medical therapy, are less than ideal.

There will naturally be exceptions to the general statements made above. An asymptomatic individual, for example, might be minimizing his actual symptoms, or might have developed symptoms so gradually that he is truthfully unaware that he is limited. Hemodynamic studies in such cases may show the need for surgical consideration. Similarly, a man with only mild symptoms under ordinary activity might have a livelihood dependent upon more strenuous physical activity and consequently might be a candidate for surgical intervention.

Auscultation. This can be most helpful in aiding the physician in deciding the type of operation indicated. A typical apical diastolic rumble following an opening snap and having presystolic accentuation ending in a loud first sound with no systolic murmur indicates predominant or pure mitral stenosis. If the opening snap is loud, the probability of a pliable valve, which can be corrected by closed surgery, is strong. If the snap is faint or absent, a calcified or otherwise nonpliable valve necessitating open repair or replacement is suggested. A holosystolic apical murmur followed by a third heart sound with or without an early diastolic rumble indicates predominant insufficiency which must be approached by open technique. Variable combinations of these findings indicate combined stenosis and insufficiency and the need for further clarification by hemodynamic studies. Care should be taken, however, not to misinterpret the systolic murmur of tricuspid insufficiency for that of a mitral leak, when indeed the patient has tight mitral stenosis. The presence of murmurs suggesting associated aortic valve lesions usually indicates the need for further hemodynamic studies.

Electrocardiography and cardiac fluoroscopy. These studies are frequently helpful in delineating specific chamber enlargement and thus may indicate whether stenosis or insufficiency is predominant or whether other valve abnormalities are present. A large right ventricle suggests predominant mitral stenosis, while left ventricular enlargement indicates associated insufficiency or some other lesion producing stress on the left side of the heart. The presence of valvular calcification seen fluoroscopically will suggest that an open surgical procedure is indicated. Kerley lines or an altered pulmonary vascular pattern may indicate pulmonary hypertension and thus, along with symptoms, help categorize the patient as being in the operable group. The detection of atrial fibrillation is not a contraindication to surgery but simply indicates the progression of the patient's status.

Embolization. The occurrence of systemic embolization throws weight toward the decision for surgical intervention but should not be used alone as the sole indication for operation. If one is certain that a repair of the valve can be accomplished, multiple embolization is an indication for operation; however, if the factors described above suggest that valve replacement may be necessary, the patient may be left with an equally prevalent tendency to embolize. Hence, in general, other signs and symptoms should be present before deciding that patients with embolic phenomena should be subjected to an operation.

Hemodynamic appraisal

There is now, and will probably continue to be, considerable variation of opinion

as to which if any patients with mitral disease should be subjected to hemodynamic studies before a final decision regarding surgery is reached. The policy in this institution is to study all patients whose symptoms suggest that they may benefit from an operation by combined right and left heart catheterization and selective cineangiography. However it is probable that the symptomatic patient with pure mitral stenosis and findings indicating a pliable noncalcified valve could be taken to surgery without such studies, particularly if facilities for standby perfusion are available if needed. Nevertheless, even the best of physicians may misjudge the significance of an aortic systolic murmur in the presence of severe mitral stenosis, or may misinterpret a systolic murmur at the apex as not representing significant mitral insufficiency. These and other problems are clarified by hemodynamic studies.

In this laboratory the right heart procedure is performed in the usual manner using a vein in the right arm. After pulmonary artery and wedge pressures as well as cardiac output measurements are obtained at rest and with exercise the venous catheter is left in the pulmonary artery and retrograde entry of the left ventricle is performed via the right brachial artery using a Sones catheter. Simultaneous left ventricular and wedge or pulmonary artery end-diastolic pressures are recorded at rest and if indicated with exercise. The venous catheter is then removed and a left ventricular angiogram in the right anterior oblique position is performed. This study allows one to document the presence of and to semiquantitate the degree of mitral insufficiency present. It also allows appraisal of the mobility and pliability of the major leaflet of the mitral valve, as well as the contractility and function of the left ventricle. The catheter is then withdrawn to the ascending aorta and a supravalvular aortogram is performed; these maneuvers allow one to ascertain the presence and degree of aortic stenosis or insufficiency. Selective coronary arteriography is then done in all patients over 40 years of age. If tricuspid disease is suspected clinically or by the right atrial pressure curves, additional angiographic study of the tricuspid valve is performed. While it is undoubtedly true that in most cases the tricuspid insufficiency associated with mitral stenosis needs no surgical repair[8] we have on several occasions, found the uncorrected tricuspid valve to be the Achilles heel of an otherwise successful mitral valve repair and we believe angiography in such instances aids in the decision as to whether the tricuspid valve should be approached surgically.

Whether all patients with mitral disease being considered for an operation should have the above, or similar studies performed is admittedly open to question. As noted above certain ideal cases of pure mitral stenosis or of isolated mitral insufficiency might well be taken to surgery without hemodynamic study. Obviously asymptomatic patients need not be studied unless some clinical finding or perhaps the physician's intuition suggests that the patient *is minimizing or does not* recognize, his symptoms. However in the cases of combined mitral stenosis and insufficiency or in cases of multivalvular disease, or suspected coronary disease such studies are certainly indicated. Cardiac surgery should not be an exploratory cardiotomy.

An actual left atrial pressure curve, or left atriogram is not felt to be necessary. The *diastolic gradient* between the left ventricle and the wedge pressure indicates the gradient across the mitral valve. A gradient of 6 to 10 mm. Hg which increases with exercise is significant but all gradients must be interpreted with respect to the flow across the valve. In the final analysis, more weight is given to the angiographic appearance of the valve than to the pressure-flow measurements.

The myocardial factor

Considerable literature has been written on the subject of the myocardial[7] versus the valvular factor in patients with mitral valve disease. This controversy presents the concept that some individuals with valve disease are disabled not because of the valve abnormality but because of a poorly functioning ventricular myocardium. While it may be true that a few such cases will be found, it is our feeling that most such cases represent not a *fault in the*

myocardium but an undiagnosed valve lesion or coronary artery disease. This is one of the most cogent reasons for the thorough hemodynamic and angiographic study of all patients being considered for an operation

Open vs. closed surgery

What patients then with mitral valve disease, should be subjected to operation and what type of operation, i e open or closed technique, should be advised? The answers to these questions, we feel lie in the correlation of a careful clinical appraisal with a thorough hemodynamic study and the relation of these findings to the natural history of rheumatic heart disease as we best know it. It must be recognized that rheumatic valvular disease has several stages. The initial stage, that of acute carditis, is a myocardial problem and obviously is not amenable to surgical valvular therapy The disease process then usually goes through a long stage where it is essentially no problem—individuals have murmurs indicating valvular disease but are totally asymptomatic under normal activity This stage is also not subject to surgical therapy except in a rare instance. The process may then become a mechanical problem and at this stage an operation can be beneficial but may not be necessary If the mechanical problem is mild i.e. if symptoms are static and do not significantly limit the individual medical therapy will be as beneficial as an operation However even at this stage other factors may supervene to tip the balance in favor of an operation. Such factors may be medical e.g. a systemic embolus or a pregnancy or they may be economic as in the case of the individual who can support his family only through strenuous physical activity which even his relatively mild condition will not permit. Progression of symptomatology however to the point where an individual has significantly limited activity is unquestionably an indication for surgical intervention. The problem remains mechanical and correction of the valve lesion will relieve the difficulties (mainly pulmonary hypertension and/or low cardiac output) created by this mechanical problem Whether this mechanical problem progresses to a myocardial problem is uncertain. We strongly feel that, even in those patients in whom a myocardial factor is felt to be present surgical correction of the valve deformity is indicated. Prognosis at this stage utilizing medical therapy alone is hopeless, and most patients will be improved by an operation. An obvious corollary to the above is that patients should not be permitted to reach this stage of the disease process.

Once the decision for surgical intervention has been made the type of operation will be determined by appraisal of all the factors noted above, and in the final analysis, by the pathology found in the operating room Generalization e.g that all cases of mitral stenosis should be done closed (or open) is not sensible. However two generalizations are in order namely to correct the problem in the safest possible manner and to repair rather than replace whenever possible. Closed valvulotomy unquestionably entails less risk than open heart surgery but unfortunately fewer and fewer patients are seen in whom this is possible. The ideal patient is one who has not been previously operated upon, who has no history of emboli who has no other valvular lesion, and in whom the evaluation outlined above suggests a pliable valve. Even in such cases we have a pump oxygenator assembled on a standby basis. Several factors strongly suggest that open surgery will be indicated These include (1) previous valvular surgery (2) demonstration of thrombus by angiography or a history of embolization, (3) a heavily calcified or otherwise nonpliable valve, (4) the presence of mitral insufficiency and (5) the presence of aortic or tricuspid valve disease. The problem of closed versus open surgery in pure mitral insufficiency does not exist since there is no satisfactory closed procedure for this lesion. Once open surgery is undertaken for either mitral stenosis or insufficiency every effort should be made to repair rather than to replace, the valve. The present prosthetic devices are prone to thrombotic and embolic problems, and deterioration of a part of the prosthetic valve has recently become known to be a factor Until a completely satisfactory artificial valve is devised, it might be better to compromise a little

result in order to preserve the patient s own valve.

Contraindications to surgery Probably the only absolute contraindication to mitral valve surgery is the presence of serious independent disease which would in itself so shorten the patient s longevity as to make surgical correction of the valve futile. Additional valvular problems can now be corrected at the time of mitral valve surgery Severe cardiac decompensation acute rheumatic carditis, bacterial endocarditis etc are only relative contraindications necessitating delay in surgery until they have been corrected so far as possible by medical therapy

Summary

In the sick patient with mitral valve disease, surgery is unquestionably an important adjunct in our therapeutic armamentarium The proper time for surgery can best be defined by correlating the clinical and hemodynamic features of the individual case with the life history of rheumatic valvular disease. Once embarked upon the operation should be done in the manner which gives the best possible result with the least risk, always preserving the patient s valve when possible.

REFERENCES

1 Ellis, L. B Abelmann, W H., and Harken, D E.: Selection of patients for mitral and ortic valvuloplasty Circulation 15:924 1957
2. Boyle, D McC.: A comparison of medical and surgical treatment of mitral stenosis, Brit. Heart J 23:377 1961
3 Ellis, L. B and Adler L. N: Criteria for surgery in mitral valvular disease, Am. J Cardiol 12 17 1963.
4. Butterworth, J S., Chassin, M McGrath, R. and Reppert, E. H. Cardiac auscultation, New York, 1960, Grune & Stratton, Inc., p. 66.
5 Morrow A. G., Harrison, D C. Ross, J J Braunwald, N Clark, W D and Ross, R. S. The surgical management of mitral valve disease. A symposium on diagnostic methods, operative techniques and results, Ann. I t. Med. 60 1073, 1964
6. Braunwald, N S., Ross, J J and Morrow A. G: The conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement, Circulation (Suppl. 1) 35:63 1967
7 Fleming, H. A., and Wood, P The myocardial factor in mitral valve disease, Brit. Heart J 21 117 1959
8. Duvoisin, G. E., Brandenberg R. O and McGoon, D C. Factors affecting thromboembolism associated with prosthetic heart valves, Circulation (Suppl. I) 35 70 1967

Annotations

Treatment of bradycardia and hypotension syndrome in patients with acute myocardial infarction

The practical clinical management of arrhythmias and cardiovascular failure in patients with acute myocardial infarction is becoming increasingly important with the advent of intensive care and coronary units. Although the occurrence of bradycardia and associated cardiovascular failure has long been recognized by clinicians, analyses of the hemodynamic changes underlying clinical syndromes and evaluation of treatment has only recently received detailed analyses.

Sinus bradycardia occurs at some time in approximately 20 per cent of patients with acute myocardial infarction. It usually becomes apparent within the first hours of illness and may be spontaneous, the result of morphine[1] or methadone administration or may be related to extreme pain. The spontaneous form is seen particularly in patients with posterior infarctions[2] but may also occur when the infarct is anterior. Ventricular bradycardia is often associated with short P-R interval, abnormal P waves, A-V dissociation, nodal rhythm, and second-degree A-V block.

When bradycardia is moderate (50 to 60 per minute) and transient, it is usually of little clinical significance. More serious consequences follow if bradycardia is profound (25 to 40 per minute), and particularly if ventricular function is poor with low stroke volume. Persistently low heart rate leads to fall in cardiac output and arterial pressure. The associated clinical syndromes vary in severity. Symptoms may be limited to a weak sensation and nausea while lying flat, but with dizziness, pallor and sweating after sitting up or standing. The symptoms and general appearance of the patient resemble those of common "vasovagal"[3] faint. If the changes progress, mental confusion may be succeeded by loss of consciousness associated with the clinical picture of profound circulatory shock. Cardiac arrest may follow.

Treatment is indicated in most patients at an early stage in view of the potential hemodynamic deterioration and also because of the increased incidence of serious arrhythmias occurring in patients in whom bradycardia is allowed to persist. Mild cases may be managed conservatively by maintaining the patient flat in bed or by raising the foot of the bed. If the heart rate does not increase and blood pressure remains low, atropine sulfare injected intravenously is often effective. In the first place, 0.3 mg. should be given followed by further 0.3 mg. increments up to a total of 2 mg., titrating the patient to a heart rate of 80 to 90 per minute. Subsequent doses are required every 3 to 4 hours. It must be emphasized that the drug should be given intravenously as absorption from subcutaneous or intramuscular injection is too slow and unpredictable under conditions of circulatory failure.

In the case of rapid clinical deterioration, the patient should lie flat and the legs should be raised 45 degrees to the horizontal by an assistant simultaneous with the administration of atropine. Under these circumstances, isoproterenol, 0.05 mg. intravenously, is also effective and is often superior to atropine in the presence of second-degree heart block. With less urgent situations, isoproterenol should be given by intravenous infusion (1 mg. per 500 ml. of dextrose) for better control and avoidance of overdose. Drug therapy of the bradycardia hypotension syndrome may often be withdrawn after approximately 12 hours, but any tendency to recur should be treated at an early stage.

The physiological mechanisms involved in bradycardia and associated cardiovascular failure are not clearly understood. Slowing of the heart may be due to a direct effect of the infarct on the pacemaker tissues. Alternatively, there may be a disturbance of parasympathetic and sympathetic autonomic activity. This is supported by preliminary measurements of urine catecholamines which show low levels of excreted norepinephrine when the heart rate is low. Reflex effects could be mediated directly from receptors in the heart, or could involve more complex nervous activity secondary to pain and anxiety. Bradycardia hypotension syndromes following morphine administration are also probably the result of central nervous system reflex activity as suggested by analytical experiment.

The mechanisms by which atropine and isoproterenol benefit the circulation are probably concerned to a large extent with increasing cardiac output and arterial pressure. Atropine[4] increases cardiac output in proportion to heart rate, the stroke volume remaining constant. Some increase in stroke volume may occur when the patients' legs are raised at the same time. Arterial pressure rise is less marked than cardiac output owing to a fall in peripheral resistance. Isoproterenol improves cardiac output both by an increase in heart rate and probably of stroke

me due to it powerf l positive inotropic effect on the heart Arterial pressure increases mainly as a result of ncreased blood flow

The side effects of tropine relat mainly to its peripheral nd central nervous effect Dry mouth is common if treatment has to be maintained Much less con monly hallucinations occur Withdrawal of the drug is curat e Atropine may be responsible for ca diac arrhythmias itself but in ou experience this ha not been seen More important is the increase cardiac excitability extras t les, nd arrhyth mias which may occur with exce-si e doses of isoproterenol. For this reason aref lly controlled intravenous infusion is the m thod of choice in administration of this drug

Jak Shillingford M D F.R.C.P
Michael Thomas M 1 M D M.R C.P
M R C C rdiov scula R search U it
Royal Postgraduate Medical School
Hammersmith Hospital
London W 12 England

REFERENCES

1 Thomas M Malmcrona, R Fillmore, S and Sh ll ngford, J P Hemodynamic effects of orph ne in patients with acute myocardial farction, Brit Heart J 27:863, 1965.
2 James T N Posterior myocardial infarction, J Michigan State M Soc. 60 1409 1961
3. Lown, B., Fakhro, A M Hood W B nd Thorn, G. W The coronary care unit, J.A.M.A. No. 3 199 156, 1967
4 Thomas, M and Woodgate D : Effect of atropine on bradycardia and hypotension in acute myocardial infarction Brit. Heart J No. 3 28 409 1966
5 Valori, C., Thomas, M and Shillingford, J P : Free noradrenaline and adrenaline excretion in relation to clinical syndromes fol lowing myocardial infarction Am. J Cardiol. 20:605 1967
6. Costa tin, L.: Extracardiac factors contribut ing to hypotension during coronary occlusion Am. J Cardiol. 11:205 1963.
7 Bergel, D H and Makin, G S. Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dogs heart, Cardiovas. Res. N 1 1:80 1967
8. Henney R. P Vasko, J H., Brawley R. K., Oldham, H N and Morrow A. G The effects of morphine on the resistance and capacitance vessels of the peripheral circulation, AM. HEART J No. 2, 72:242, 1966.
9 Wilson, F H The production of atrioventricu lar hythm in man after the administration of tropin, Arch I t. Med 16:989 1915.

The long term administration of intravenous antibiotics in endocarditis

The various practical problems of long term intra enous therapy hav been met repeatedly i the treatment of bacterial endocarditis when t is often necessary to administer antibiotics, particularly penicillin in ery high dosage for long periods of time.[1] W th duration of treatment of six weeks, patients find the intra enou rout preferable to repeated intramuscular jections.

There are tw pproaches for the long-term intra enous administration of ntibiotics by large vei or caval catheterization nd by cannulas or needles situated in the smaller peripheral veins. The high risk of septic thrombosis and other hazards of large vein or ca l catheterization ha e been described by McN ir and Dudley wh reported that of a series of patient who underwent ca l catheterization in nine of the leven patients who died, death was contributed to by this procedure The incidence of complication is higher when the lower limb is used for the cut-down. Another tudy has shown that pathogens could be cult red from 52 per cent of catheter tips left in the caval position for 48 hours or more. It is undesirable t ntroduce these hazards in a group of patients who are particularly vulnerable to the possible sequelae and it would seem preferable to use small peripheral veins where complications are of less magnitude if they occur

The factors which influence the development of thrombophlebitis part from the nature of the infusion fluid are the duration of the infusion and trauma to the vein. Limitation of infusion time t one sit necessitates repeated venepuncture of small veins and the needle that has been found to be very suitable for this l being minimally trau matic is the inf t scalp ein needle. These needles are thin-walled with wider lumens than the equi alent gauge tandard needles. An adequat flow rate can be maintained and they are suitable for blood or packed-cell transfusion

In treating series of ten patients with bacterial endocarditis the Baxter small ei set (23 gauge)

and the Sterilon (22 gauge) were used. They proved satisfactory for the long term administration of intra enous antibiotics.

I this series, the sit of infusion was hanged at approximately tw to three day intervals and thrombophlebitis was rare occurrence. Occasionally the infusion slowed or stopped before this time, but restarted when moved t another vein. It was found that, if reaction occurred it was of minor importance in a small peripheral vein which could then be "rested. As many veins as possible should be tilized in rotation.

One liter of fluid daily as ehicle for the antibiotic is adequate and the nature of this depends on the patient electrolyte state and cardiac condition but care should be observed with the mount of saline infused

Doses of up to 50 megaunits of penicillin daily may be given, or indeed a higher dose if this is thought to be desirable Streptomycin is sometimes added for broader spectrum and synergistic action. I one patient, the infusion was maintained at one site for 27 days without complication in another the infusion was frequently removed at night, allowing ndisturbed sleep free from the infusion apparatus. Thus, it is suitable technique of intermittent antibiotic therapy is considered preferable

These needles were found to be more suitable for repeated enepuncture than plastic or metal cann las because they are less traumatic to the ein and simpler and quicker to set up. The advantage is clear from the little apprehension the patient shows and minimal pain he experiences when the infusion site is to be changed.

Attached to each needle is length of light polythene tubing with an adaptor on the end. A plastic butterfly flange incorporated at the junction of needle and tubing is an advantage in securing the needle firmly with the skin and preventing rotation. After cleaning the skin over the selected vein, the needle, held for maneuverability at its base by the tip of straight blunt Spencer Wells forceps, is advanced through the skin and passed short way along the vein, needle and tubing are secured by strapping to the skin.

Scalp vein needles have found a place in other fields of adult practice notably in treating patients with difficult veins or veins which be become difficult because of long-term intra enous therapy for example, with postoperativ complications or when repeated frequent transfusion is necessary blood diseases. They ha e also proved an ad antage in patients who need long term intravenous fluid therapy when the daily calorie and electrolyte requirements may be administered in the day time, so that the infusion may be removed at night. This ensures good night rest and has helped in maintaining morale.

C. F. P. Wharton M. A. B.M.
Registrar Cardiac Department
G y Hospital
London S.E. 1 England

REFERENCES

1 Louria, D. B. The treatment of endocarditis AM. HEART J 66:129 1963.
2 Dormer A. E The treatment of bacterial endocarditis, Brit. M B II. 16:61 1960.
3 M Nair T J and Dudley H. A. F Local complications of intravenous therapy Lancet 2:365 1959
4 Jones, P F I travenous infusion techniques, P oc. Roy Soc. Med 60 72, 1967
5 Druskin, M S., and Siegel, P D Bacterial contamination of indwelling intravenous polyeth lene catheters, J.A.M.A. 185:966 1963.
6. Bolton Carter J F Reduction of thrombophlebitis by limiting duration of intra enous infusions, Lancet 2:20, 1951
7 Wharton, C. F P Infant scalp vein needles in the intravenous treatment of endocarditis in adults, Brit. M J 2 702 1967
8. Nagamm, H. F Infant scalp ein needles, Brit. M J 3:48, 1967
9 Holliday Rhodes, A. D Infant scalp vein needles, Brit. M J 3:310, 1967

Cardiac pacing in the management of advanced heart block during acute myocardial infarction

The mortality rate is high from advanced atrioventricular block associated with acute myocardial infarction. I this article, fiv cases of third-degree heart block associated with acute myocardial infarction hav been treated by introduction of a Silastic Short Term Transvenous Cardiac Electrode Catheter (Model 5821-C Chardack) int the right entricular cavity These patients all showed signs of bock ith bradycardia hypotension oliguria, and peripheral signs of shock. Four of the five cases returned to normal sinus rhythm within the first ten days, the erage duration of pacing being 6.7 days. It is felt by the author that this is the preferred w y of managing high-grade heart block associated with acute myocardial infarction These fiv cases were reported with 23 cases reported in the literature and compared favorably with them in the response t endocardial pacing and the decrease in mortality rate compared w th drug therapy of this syndrome. The mortality rate in this group is 25 per cent, con-

this infection, cases of Q fever endocarditis have been reported in detail by Robson and Shimmin, Andrews and Marmion, Evans and co-workers,[10] Smith and Evans,[11] Marmion and associates,[12] Ferguson and colleagues,[13] McIver[14] Postgraduate Medical School Clinicopathological Conference,[15] Mitchell and co-workers,[16] and additional cases have been briefly mentioned by others.[17-23] Although all these cases were reported from Britain or Australia, it seems likely that similar cases occur elsewhere—indeed two probable cases in California were investigated some years ago.[24] The diagnosis of Q fever endocarditis has certain difficulties, but its recognition is important because of the poor prognosis the rickettsiae resist available bactericidal therapy and are not eradicated by bacteriostatic drugs. The following survey is based on the nine fully reported cases together with two additional cases which will be reported elsewhere.[25,26]

The ages of the 11 patients ranged from 33 to 60 years, most being in the fifth decade ten were men, one was a woman. Previous rheumatism was recorded in four and possibly in another two (Table I). The affected valves had been subjected to previous operation in t patients.[11,14] The onsets of illness varied, were sometimes insidious but often showed acute or variable period of fever followed usually after an interval ranging from few months to over year by overt cardiac disease. The stage of cardiac illness lasted from 3 months to 2 years or more, commonly with variable fever asthenia, finger clubbing manifestations of heart failure, and changing cardiac murmurs. Thrombotic or embolic phenomena were not always present, but several cases showed purpuric rash on the lower limbs. Broad-spectrum antibiotics often reduced fever and caused temporary clinical improvement but death eventually supervened in all patients from heart failure or from acute vascular catastrophe of lung or brain

There was usually moderate anemia (Hb 10.0 to 13 1 grams per cent), leukocyte counts were low or normal, and one patient had thrombocytopenia.[16] The erythrocyte sedimentation rate (ESR) was usually raised (22 to 122 mm in the first hour). Plasma proteins were elevated with increased globulins which, when tested, were gamma globulins. Hobbs and associates[27] report a predominantly IgM response probably due to continued intravascular stimulation with particulate antigens. Albuminuria was found in about half the patients but blood cells were not usually present in urine.

When the diagnosis was made in life, it was based on very high (often over 1/1,000) complement fixation titers of serum antibody to the usual Phase II diagnostic antigen of *Rickettsia burneti*, together with similar titers of antibody to Phase I antigen which is characteristic of chronic Q fever These tests may show prozone which can result in false negatives

Major illness	*Rickettsiae isolated*			*R burneti C.F titers*	
	Blood	*Valve*	*Other*	*Phase I*	*Phase II*
Fever; aortic incompetence	+	Aortic	Spleen liver	1 000	2 000
Finger clubbing and splinter hemorrhages aortic systolic murmur cardiac failure	NT	Aortic	Spleen	"low	64
Fever anemia hepatosplenomegaly finger clubbing mitral stenosis cardiac failure	NT	Mitral	—	256	256
Convulsions finger clubbing mitral stenosis aortic incompetence renal and congestive cardiac failure	NT	Mitral		256	64
Fever hepatosplenomegaly finger clubbing aortic incompetence congestive cardiac failure	—	Aortic	Liver kidney	6 400	6 400
Fever leg embolus aortic incompetence anginal attacks, last one fatal	—	Aortic	Spleen	128	256
Aortic incompetence cardiac, splenic and pulmonary infarcts changing murmurs	NT	A.M †	NT	2 000	4 000
Fever dyspnea and angina purpura on legs and trunk	NT	Aortic	Spleen liver	1 280	1 280
Icterus purpura on thighs hepatosplenomegaly fever aortic incompetence and cardiac failure	NT	Aortic	NT	1 024	2 048
Fever; attacks of l ventricular failure purpura mainly on lower limbs	—	Aortic	—	2 048	2 048
Aortic incompetence and finger clubbing congestive cardiac failure	+	Aortic	—	400	200

unless higher serum dilutions are also tested. Antibody may also be detected by immunofluorescence.[8] Sometimes rickettsiae may be isolated by inoculation of guinea pigs with blood.[7]

The aortic valve was affected in 10 cases, the mitral in three (both were involved in 2 cases). The degree of endocarditis varied from an inconspicuous row of tiny vegetations on the cusps of the affected valve[13] to gross valve distortion with large fungating vegetations, ulceration, and aneurysms in the ventricular wall. Microcolonies of rickettsiae and scattered extracellular organisms were present, often patchily in the diseased area, demonstrable best by Giemsa or Macchiavello staining. Immunofluorescent staining by specific rickettsial antibody may also be helpful.

Specific diagnosis post mortem may also be achieved by isolating rickettsiae from unfixed vegetations, or serologically by testing for Phase I and Phase II-reactive antibodies in serum, ascitic, or pleural fluid.

Diagnosis of Q fever endocarditis depends on clinical awareness of the condition. Bacteriologically undiagnosed cases of infective endocarditis should be investigated serologically. Since it seems possible that bacteria might infect heart valves damaged by rickettsial endocarditis and that rickettsiae might invade valves damaged by bacterial endocarditis, serological investigation would also be appropriate for bacteriologically positive infective endocarditis cases in which the clinical response to antibacterial therapy is unsatisfactory.

The usual ineffectiveness of antibacterial drugs suggests that surgical excision deserves consideration in these cases. Since the preparation of this paper Kristinsson and Bentall[20] have reported 6 cases of patients who survived for periods from 3 months to 2 years after treatment by operation (5 patients—4 by replacement of aortic valves by Starr-Edwards prostheses, one by relief of subvalvular obstruction) and/or tetracycline (5 received long-term therapy of 1 gram daily, the other received chloramphenicol for two weeks followed by intermittent courses of tetracycline for 2 months before operation). Of these patients, one died from coronary occlusion 6 months after operation, showing no macroscopic signs of infection. These results suggest that excision of infected tissues may eradicate the disease and prevent death, and emphasize the importance of diagnosing this condition.

The frequency of Q fever endocarditis is difficult to estimate. Marmion and associates[12] found only one case among 35 bacteriologically negative cases studied in England. I found none in a series of 104 patients in Scotland with suspected endocarditis, but in only 14 of these was endocarditis confirmed and only 7 of this group had negative blood cultures. The frequency might be higher in areas where Q fever is more prevalent, particularly where the population is exposed to sheep or cattle or their products. Occupational exposure to these animals or their dung or birth products appears to be inadvisable for persons with damaged heart valves, and perhaps it is for such persons that a prophylactic rickettsial vaccine might prove useful.[16]

Q fever endocarditis is uncommon but not rare. The main features of the disease are reviewed. Because the infection resists available antibacterial drugs, the prognosis is bad. Excision of infected tissue and prosthetic replacement of the diseased valve offers a hope of cure. Specific diagnosis can be made by serological tests which should be carried out in cases of suspected endocarditis with negative blood cultures or in which the response to antibacterial therapy is unsatisfactory.

N. R. Grist, B.Sc., M.B., Ch.B., F.R.C.P.E.,
F.C. Path.
University Department of Infectious Diseases
Regional Virus Laboratory
Ruchill Hospital
Glasgow, Scotland

REFERENCES

1. Uwaydah, M. M., and Weinberg, A. N.: Bacterial endocarditis—A changing pattern, New England J. Med. 273:1231, 1965.
2. Lerner, P. I., and Weinstein, L.: Infective endocarditis in the antibiotic era, I, New England J. Med. 274:199, 1966.
3. Lerner, P. I., and Weinstein, L.: Infective endocarditis in the antibiotic era, II, New England J. Med. 274:259, 1966.
4. Lerner, P. I., and Weinstein, L.: Infective endocarditis in the antibiotic era, III, New England J. Med. 274:323, 1966.
5. Lerner, P. I., and Weinstein, L.: Infective endocarditis in the antibiotic era, IV, New England J. Med. 274:388, 1966.
6. Hughes, P., and Gauld, W. R.: Bacterial endocarditis. A changing disease, Quart. J. Med. 110:511, 1966.
7. Marmion, B. P., Stoker, M. G. P., McCoy, J. H., Malloch, R. A., and Moore, B.: Q fever in Great Britain: An analysis of 69 sporadic cases, with a study of the prevalence of infection in humans and cows, Brit. M. J. 1:503, 1953.
8. Robson, A. O., and Shimmin, C. D. G. L.: Chronic Q fever. I. Clinical aspects of a patient with endocarditis, Brit. M. J. 2:980, 1959.
9. Andrews, P. S., and Marmion, B. P.: Chronic Q fever. II. Morbid anatomical and bacteriological findings in a patient with endocarditis, Brit. M. J. 2:983, 1959.
10. Evans, A. D., Powell, D. E. B., and Burrell, C. D.: Fatal endocarditis associated with Q fever, Lancet 1:864, 1959.
11. Smith, W. G., and Evans, A. D.: Chronic Q fever with mitral-valve endocarditis, Lancet 2:846, 1960.
12. Marmion, B. P., Higgins, F. E., Bridges, J. B., and Edwards, A. T.: A case of subacute rickettsial endocarditis; with a survey of cardiac patients for this infection, Brit. M. J. 2:1264, 1960.
13. Ferguson, I. C., Craik, J. E., and Grist, N. R.: Clinical, virological, and pathological findings in a fatal case of Q fever endocarditis, J. Clin. Path. 15:235, 1962.
14. McIver, M.: A case of Q fever endocarditis, M. J. Australia 2:379, 1962.
15. Clinicopathological conference: An unusual case of endocarditis demonstrated at the Post

graduate Medical School of London, Brit. M. J. 1:1143, 1963.
16. Mitchell, R. Grist, N. R. Bazaz, G. and Kenmuir A. C. F. Pathological, rickettsiological, and imm. fl orescence studies of case of Q fever endocarditis, J. Path. & Bact. 91:317 1966.
17. Marmion, B. P. Subacute rickettsial endocarditis. An unusual complication of Q fever J. Hyg. Epidemiol. Microbiol. & Imm nol. 6 79 1962.
18. Evans, A. D. Q fever The Practitioner 191:605 1963
19. Grist, N. R., Ross, C. A. C., and Sommerville, R. G. Bacterial endocarditis. A changing pattern (Corr.) *Lancet 1 727 1967*
20. McSwiggan, D. A. Bacterial endocarditis. A changing pattern (Corr.) Lancet 1:956, 1967
21. Hobbs, J. R., Sommerville, R. G., and Mc Swiggan D. A. Rickettsial endocarditis and IgM globulin, Lancet 1 1108, 1967
22. Beck, M. D. Bell, J. A., Shaw E. W. and Huebner R. J.: Q fever studies in southern California. II A epidemiological study of 300 cases, Pub. Health Rep. (Wash.) 64:41 1949
23. Lamb, D. C., and Grist, N. R.: A case of Q fever endocarditis, Brit. M. J. 4:418, 1967
24. Lamb, R., Boyd, J. F. and Grist, N. R. Q fever endocarditis. Report of case. I prepa ration
25. *Kristinsson, A. and Bentall H. H.: Endocarditis due to Q fever.* Medical and surgical treatment, Lancet 2:693 1967
26. Marmion, B. P. (Discussion) First international conference on vaccines against viral and rickettsial diseases of man *(P.A.H.O.* Scientific Publication No. 147 Pan American Sanitary Bureau, Washington) 1967 p. 533

Letters to the Editor

Arrhythmias and synchronous pacemaker

To the Editor

In the article by Adelman and Lopez "Arrhythmias associated with asynchronous pacemaker" the authors reach two conclusions which may not be correct.

The first conclusion is that failure of synchronization *with atrial pacemaker block is due to fibrosis* around the atrial electrodes. There is no evidence that perielectrode fibrosis reduces the electrical signal sensed by the electrode unless a very large area of the atrium is fibrosed.

The second conclusion made by the authors is that ventricular ectopic beats trigger the pacemaker through an accessory ventricular electrode. The circuitry is such that neither of the ventricular *electrodes can stimulate the delay-circuit, which* to send an impulse to the ventricle. A much more likely cause of the phenomenon observed is direct triggering of the atrial pick-up by the ventricular signal sensed by the atrial leads. This, in fact, is a recognized problem in atrial triggered pacemakers as a stimulus reaching the atrial electrodes with great enough intensity will trigger the unit.

Thomas I. Preston, M.D.
National Heart Hospital
Westmoreland Street,
London W 1 England

Reply

To the Editor

This is in reply to the letter by Dr Preston related to our article "Arrhythmias associated with synchronous pacemaker." I would like to say that we did not reach a conclusion with respect to the two points mentioned by Dr Preston. We merely suggested two possibilities. I would like to discuss these two points separately.

The first point is related to atrial-pacemaker block. The most common cause of this syndrome is failure of the power pack. This was the obvious cause in one of our patients. After the paper was submitted for publication we have had the opportunity of studying five more patients with the same syndrome. After the power pack has been changed the atrial-pacemaker block has disappeared. However, there are two patients in our group in which in spite of a new power pack the atrial portions have been working only intermittently. This, in our opinion, is not evidence, but is suggestive of interference of transmission of the sinus impulse *to the atrial pick-up (perhaps due to fibrosis).*

With respect to the second point, we would like to say that unfortunately we do not know very much about the circuitry of this type of pacemaker. It is possible that theoretically the circuitry is such that neither of the ventricular electrodes can stimulate the delay circuit. In our opinion Dr Preston's explanation of the phenomenon observed is incorrect because of the following facts: (1) If *the ventricular premature beats were to trigger* directly the atrial pick-up, we would see retrograde P waves following these beats. We did not see any retrograde atrial activation; in fact, as stated in the paper, there was no relationship between the P waves and the ventricular ectopic beats. (2) To reach the atria a ventricular premature beat must be conducted in a retrograde fashion along the conducting tissue. However, these patients have complete *atrioventricular block.* This block is not only in the forward but also in the retrograde direction. The latter is demonstrated by the fact that the asynchronous impulses of the artificial pacemakers could depolarize the ventricles but are not conducted to the atria. (3) Assuming that the ventricular premature beat could reach the atria by an "unknown" mechanism and assuming also that the atrial pick-up could be triggered, this signal *could not activate the power pack* because, as stated in the paper, this phenomenon was observed when the patient had a complete atrial-pacemaker block.

We are not convinced that our explanation is correct, however we are still waiting for a better one.

Jose F. Lopez, M.D.
University of Saskatchewan
Department of Medicine
Saskatoon, Canada

Book reviews

THE BLOOD SUPPLY OF THE LOWER LIMB BONES IN MAN. By Henry V. Crock, M.B., B.S., F.R.C.S., F.R.A.C.S., with the assistance of Carmel Crock, M.B., B.S., Edinburgh & London, 1967, E. & S. Livingstone Ltd., 103 pages. Price $18.00.

This is a very good book. The author has provided concise and clear description of the circulation to the bone of the legs and feet of man. Unfortunately a study of the circulation to bone has been neglected for decades. This is due in large part to difficulties offered in a quantitative investigation of blood flow to bone. Although Mr. Crock has failed to provide measurements of blood flow, he does present excellent colored plates of injection studies of the distribution of blood vessels to bones and joints. The venous side is shown as well as the arterial. The clinical presentations are mainly from the orthopedic point of view. Even though this monograph neglects physiologic considerations, the anatomic presentations in many figures are well done and the bibliography is good. This book is highly recommended.

PREVENTION OF ISCHEMIC HEART DISEASE. PRINCIPLES AND PRACTICE. Compiled and edited by Wilhelm Raab, M.D., Emeritus Professor of Experimental Medicine, University of Vermont, Springfield, Ill., 1966, Charles C Thomas, Publisher, 466 pages. Price $25.50.

This book is based largely on the proceedings of the First International Conference on preventive cardiology held in August, 1964, at the University of Vermont, Burlington, Vt. There are 96 contributors to 58 chapters in the compilation. It would be impossible to review the many areas covered by this book but the basic theme is provided in the prologue to a condensed survey of the contents. As explained in the introduction, this book is devoted to the problem of myocardial vulnerability of the heart muscle and not to the already abundantly but still inconclusively explored problem of atherogenesis. It directs attention primarily to those long disregarded contributory neurogenic and hormonal, functional, and metabolic factors which (usually but not necessarily in conjunction with coronary atherosclerosis) possess fundamental pathogenic significance and appear rationally amenable to systematic prevention.

Certainly every physician should be familiar with the work and current thought on the areas dealt with in this book and perusal of its contents could be most rewarding. For the average clinician, however, many of the presentations will prove to be of very minor interest.

CEREBRAL VASCULAR DISEASES. Transactions of the Fifth Conference held under the auspices of the American Neurological Association and the American Heart Association, Princeton, N. J., January, 1966. Clark H. Millikan, Chairman, Robert G. Siekert and Jack P. Whisnant, Editors, New York, 1966, Grune & Stratton, Inc., 278 pages. Price $1.75.

This book offers a collection of selected presentations and discussions dealing with topics related to cerebrovascular disease. In no way could it be viewed as comprehensive coverage of current facts or concepts. The topics presented are of interest, however, and include the following: Vascular disease in animals, epidemiology of cerebrovascular disease, hypertension and cerebrovascular disease, thermography, bruits, dental ophthalmodynamometry, cerebral blood flow, blood sludging, experimental cerebral infarction, vasodilation drugs in progressive cerebral infarction, arteriovenous oxygen difference during surgery, subarachnoid hemorrhage, surgery for occlusive cerebrovascular disease.

For those interested in cerebrovascular disease, this volume provides interesting reading. The clinical cardiologist, however, is unlikely to gain much of immediate practical importance.

CHRONIC AND CONSTRICTIVE PERICARDITIS. By David H. Spodick, M.D., Assistant Professor of Medicine, Tufts University School of Medicine, New York, 1964, Grune & Stratton, Inc., 369 pages.

This reviewer had the privilege of reading in detail a companion book by this author (*Acute Pericarditis*, Grune & Stratton, Inc., 1959). It was found to be outstanding in simplicity of style yet amazingly complete in content. So it is with this more recent small volume dealing with chronic pericarditis.

To evaluate in detail the current [illegible] as is noted in most book reviews [illegible] flaws. Suffice it to say that this book should be read by all those dealing with diseases of the heart.

Announcements

FIVE DAY CONGRESS IN CARDIOLOGY will be held in Mexico Oct 29 through Nov 2 1968 the week after the Olympic Games.

The faculty will be composed of Abdo Bisteni, M D Mexico P G F Nixon, M R C P London Joseph K Perloff M D Washington and Jose Ponce de Leon, M D Mexico The Congress will be directed by Demetrio Sodi Pallares, M D Mexico, and Henry J L Marriott, M D St. Petersburg.

For further details write the Rogers Heart Foundation, 500 First Federal Building St. Petersburg, Fla

THE SECOND ANNUAL WORKSHOP IN ELECTROCARDIOGRAPHY sponsored by the Rogers Heart Foundation, will be held at The Tides Bath Club, Redington Beach Fla June 17 through 21 1968. The Director will be Henry J L Marriott, M D

For further details, write the Rogers Heart Foundation, 500 First Federal Building, St. Petersburg, Fla.

Author index*

Subject index*

January pp. 1-144 February pp. 145-28 ; March, pp. 283-34 April, pp. 435-578; May pp. 579-722 June pp. 723-868

D

E